The American Journal of Medicine

July 1946

THE YORKE PUBLISHING COMPANY, INC.
49 WEST 45TH STREET · NEW YORK 19, N.Y.

The American Journal of Medicine

The American Journal of Medicine is published monthly by The Yorke Publishing Co., Inc., 49 West 45th Street, New York 19, N. Y. Yearly Subscription, $10.00 U. S. A.; $12.00 Canada; $12.00 Foreign. Single Numbers $2.00; Special Numbers $4.00. Application for Second Class Entry July 1, 1946, at the Post Office, New York, N. Y., and on July 1, 1946, at York, Pa., under the act of March 3, 1879 is pending. July, 1946—Volume 1, No. 1.

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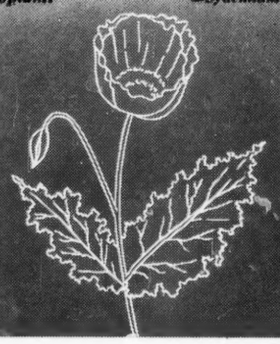

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Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p.186.

Batterman, R. C., and Mulholland, J. H.: Arch. Surg. 46:404, 1943.

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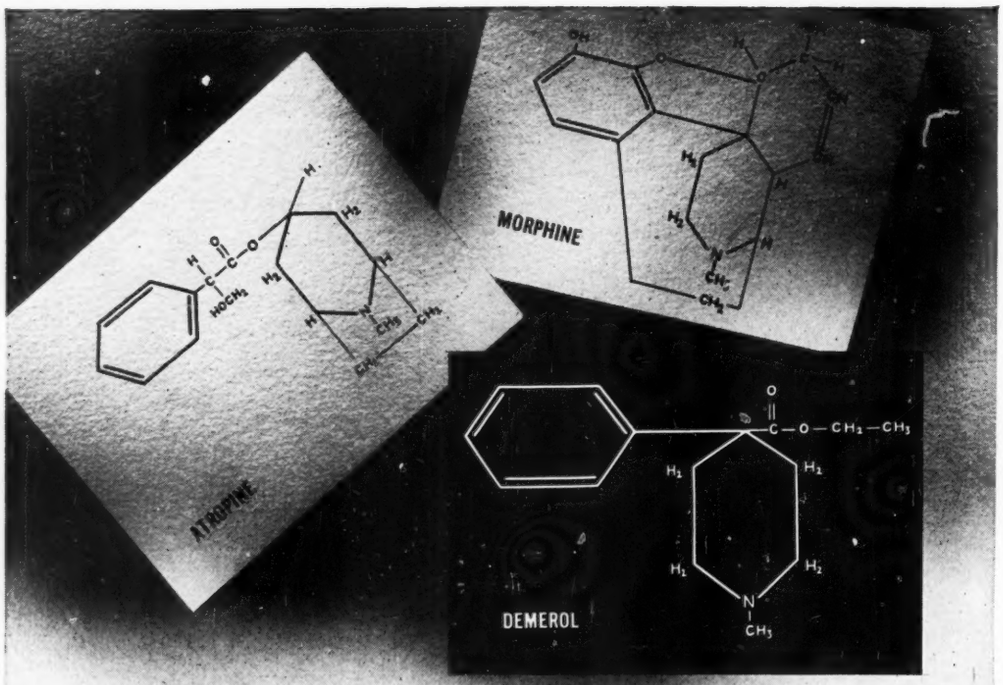

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The American Journal of Medicine

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General Information

THE AMERICAN JOURNAL OF MEDICINE extends an invitation to the profession for original releases on clinical investigations, clinical reviews, case reports and articles designed for postgraduate teaching.

Articles are accepted for publication with the understanding that they are original contributions never previously published. All manuscripts are subject to editorial modification, and upon acceptance become the property of THE AMERICAN JOURNAL OF MEDICINE.

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BANCROFT, F. W., STANLEY-BROWN, M. and QUICK, A. J. Postoperative thrombosis and embolism. *Am J. Surg.*, 26: 648, 1945.

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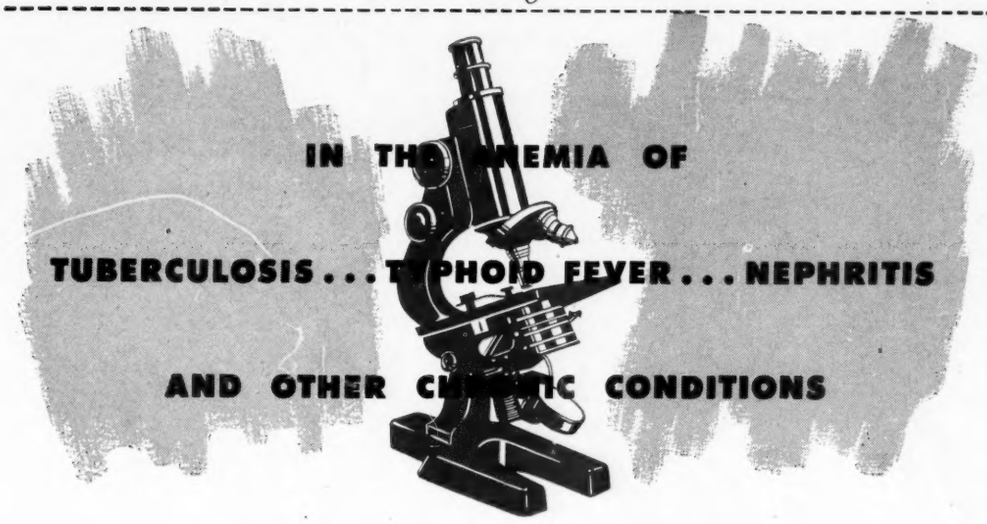

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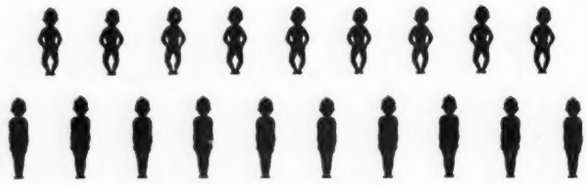

Study found Rickets in 9 out of 19

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*J.A.M.A., *129*: 1080, Dec. 15, 1945

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The American Journal of Medicine

VOL. 1 JULY, 1946 NO. 1

Editorial

The Objectives of The American Journal of Medicine

THIS issue introduces the American Journal of Medicine, a journal established to help meet certain specific needs arising from the rapid growth and development of medical research and practice. It is fitting to initiate the activities of the new publication with a statement of its aims and objectives.

One reason for launching the American Journal of Medicine at this time is to add to the available media for publication of the results of sound clinical investigation. This country already possesses a number of excellent medical journals dedicated to this end and they have performed and continue to perform a vital service in the dissemination of medical information. The capacity of existing facilities to provide full and speedy publication is, however, becoming overtaxed. Before World War II brought about some curtailment, leading medical journals were lagging behind in their efforts to keep up with the number of articles submitted and deemed worthy of acceptance. Now that normal activities are being resumed, indications again point to inadequacies in publication facilities. The load has been increased by the considerable number of medical studies carried out under wartime agencies, hitherto restricted but now being released. A further increase in the demand for publication facilities is expected to result from the enlarged programs for medical research now being put into effect with increased public and private funds. Adequate provision for the dissemination of information from these sources appears not to have been made, though it is generally recognized that for maximal effectiveness the result of these research programs should be made promptly and generally available to investigators and practitioners.

A principal objective of the American Journal of Medicine is to participate in the currently expanded program for advanced medical education at the postgraduate level. It is not necessary to dilate here upon the long-felt need for integrated postgraduate instruction, more acute now than ever before because of the increasing tempo of advance in both diagnostic and therapeutic methods. To be sure, the most effective teaching is that obtained by personal participation in the activities of highly organized medical schools and teaching hospitals and clinics. Such instruction is available to relatively few, however, and then usually only for short periods. The teaching opportunities of the medical periodical are therefore very great even though, it must be admitted, often inadequately realized. The

policy of the American Journal of Medicine will be to make full use of these opportunities by publishing articles and reviews designed largely for instruction at a postgraduate level. Some of these will take the form of integrated seminars, six of which (appearing in consecutive issues) will cover different aspects of one broad topic. The subjects selected will be chosen on the basis of timely interest, rapid development and practical ramifications. The therapeutic use of antibiotics, the first general topic selected for treatment in this way, would certainly appear to satisfy these requirements.

Special cognizance will be taken of the problems of progressive therapeutics. The recent development of chemotherapeutic and antibiotic agents for the treatment of numerous infections, the synthesis of new drugs possessing potent pharmacologic actions, the preparation of new hormones and vitamins—to keep abreast of these advances, many of immediate practical application, is a difficult yet necessary task. To assist in this endeavor, the American Journal of Medicine has arranged with the Departments of Medicine and Pharmacology, Cornell University, to publish six of the Cornell University Therapeutic Conferences each year. These exercises, which have justly attracted widespread interest and approbation, will appear in alternate issues. The intervening numbers will contain a new feature, clinics combining the presentation of medical problems with basic aspects of the disease mechanisms involved. These combined clinics, published by arrangement with the Department of Medicine, Columbia University, will provide a logical and constructive approach to certain problems of disease.

The present issue is representative of the format and typography planned for the American Journal of Medicine, which will be the counterpart in this respect of the American Journal of Surgery.

The American Journal of Medicine thus embarks upon its career. Its sponsors hope that it will merit and receive the support of those in sympathy with its aims and aspirations.

ALEXANDER B. GUTMAN, M.D.

Clinical Studies

Homologous Serum Hepatitis and Infectious (Epidemic) Hepatitis*

Studies in Volunteers Bearing on Immunological and Other Characteristics of the Etiological Agents

JOHN R. NEEFE, M.D.,†

SYDNEY S. GELLIS, M.D. *and* JOSEPH STOKES, JR., M.D.

PHILADELPHIA, PENNSYLVANIA

In a previous report,[1] the pertinent literature was reviewed and the results of preliminary studies suggesting antigenic and other differences in the etiological agents of homologous serum hepatitis and infectious (epidemic) hepatitis were described. The present report deals with additional studies which confirm and extend the preliminary observations.

MATERIALS, METHODS AND GENERAL PROCEDURE

A. *Etiological Agents.* The hepatitis viruses used in these studies were obtained from three different immediate sources:

1. *Virus SH.* This virus was present in the pool of mumps convalescent plasma that has been described in previous reports as plasma A.[1,2] It probably is the same virus that, as a result of its presence in certain lots of yellow fever vaccine, was responsible for a large outbreak of hepatitis in the United States Army in 1942.[1] This virus (in plasma A) consistently produced acute hepatitis in volunteers two to four and one-half months after its parenteral injection. As this syndrome is characteristic of that described as homologous serum hepatitis or jaundice,[1,2,3] the causative agent will be referred to herein as virus SH (virus, serum hepatitis). The following human biological materials related to this virus were used for the studies in volunteers:

(a) *Plasma A:* The origin and preparation of this pool of mump convalescent plasma and the probable relationship between the hepatitis agent it contained and that in the icterogenic lots of army yellow fever vaccine have been described in detail elsewhere.[1,3] (b) *Feces Pools* 1, 2, *and* 3 *FSH:* These preparations also have been described in detail in a previous report.[4] Briefly, these pools were composed of feces specimens obtained from six volunteers during various stages of acute hepatitis that had been induced by parenteral injection of virus SH (plasma A). In addition to the crude preparations, a bacteriologically sterile Seitz filtrate of a mixture of feces pools 2 and 3 FSH was employed in one of the present studies. (c) *Nasopharyngeal washing pool* 1

* From the Departments of Pediatrics and Medicine, School of Medicine, University of Pennsylvania. These investigations were conducted under the Commission on Measles and Mumps, Army Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, United States Army.

† National Research Council Senior Fellow in the Medical Sciences: Instructor in Medicine, School of Medicine, University of Pennsylvania.

NPSH: This consisted of a pool of the saline washings from the nose, pharynx and throats obtained from two volunteers on the fifth and thirteenth day, respectively, of acute hepatitis due to parenterally injected virus SH (in plasma A). The washings were frozen immediately after collection and were stored at −20°C. until used. (d) *Urine pool* 1 *USH* This consisted of a pool of four urine specimens collected (without preservative) between 10:00 P.M. and 8:00 A.M. on each of four successive nights from one volunteer from the ninth to the thirteenth day of acute hepatitis induced by the parenteral injection of virus SH (in plasma A). Each specimen was frozen immediately after collection and the four specimens were stored at −20°C. until used. Prior to use, the specimens were thawed and equal quantities from each were pooled to form pool 1 USH.

2. *Virus I. H., Pa.* This virus was responsible for an epidemic of infectious hepatitis that occurred during the summer of 1944 at a civilian summer camp in Pennsylvania.[5] In this epidemic, the virus was transmitted to the majority of the persons by contaminated drinking water. In volunteers, this virus consistently produced acute hepatitis eighteen to thirty-seven days after its entry by the oral route. As the syndrome was typical of that referred to as infectious hepatitis and the virus was encountered in Pennsylvania, it will be referred to herein as virus I. H., (Pa.). The following materials related to this virus were used for the studies in volunteers: (a) *Feces pool* 1 *FIH:* This preparation consisted of feces specimens obtained from four persons during the early stages of acute infectious hepatitis contracted at the summer camp mentioned above. The origin and preparation of this pool and a *Seitz filtrate* derived from it have been discussed in detail in a previous report.[5] (b) *Feces pool* 3 *FIH:* This has been described in an earlier report[4] and consisted of a pool of single specimens of feces obtained from two volunteers approximately three weeks (thirty-third and forty-third days of disease, respectively) after the disappearance of jaundice due to orally administered virus I. H., (Pa.). The pool was prepared in the same manner as pool 1 FIH and was stored at −20°C. until used. (c) *Feces pool* 7–8 *FIH:* This consisted of a pool of feces specimens obtained from each of four volunteers during the early stages of infectious hepatitis induced by the *parenteral* injection of virus I. H., Pa. (pool 2 SIH). The preparation contained portions of each of the following specimens: (1) two specimens obtained from one volunteer during the week prior to the onset of hepatitis; (2) thirteen specimens obtained from the four volunteers during the first week of the disease; (3) six specimens from three of the volunteers during the second week of the disease; (4) four specimens obtained from two of the men during the third week of the disease. The pool was prepared in the same manner as that described elsewhere in connection with the preparation of feces pool 1 FIH.[5] (d) *Serum pool* 1 *SIH:* The origin and preparation of this pool have been described in detail elsewhere.[5] This pool consisted of eight sera obtained during the first or second weeks of the disease from eight patients with infectious hepatitis acquired at the summer camp and due to virus I. H., (Pa.). (e) *Serum pool* 2 *SIH:* This pool, which has been described in detail elsewhere,[5] consisted of thirty-nine serum specimens obtained from four volunteers before and after the onset of hepatitis induced by the oral administration of feces pool 1 FIH (containing virus I. H., Pa.). (f) *Nasopharyngeal washings, pools* 1 *and* 2 *NPIH:* These pools were prepared from nasopharyngeal washings obtained from patients with hepatitis due to virus I. H., Pa. who had acquired the disease during the summer camp epi-

demic. The two pools included specimens from twenty-six patients collected at all stages of the disease. The details concerning the specimens and preparation of the pools have been described elsewhere.[5] (g) *Urine pool* 1 *UIH:* This consisted of portions of urine specimens collected from thirty-eight patients with hepatitis due to virus I. H., Pa. who had acquired the disease during the summer camp epidemic. The details concerning the specimens and preparation of the pool have been presented elsewhere.[5]

3. *Virus I. H., S.* Feces containing this virus were provided for these studies by Dr. W. P. Havens and Dr. J. R. Paul. The origin and properties of this virus have been described in detail in a recent report by Havens.[6] The virus originally was obtained from the feces of a United States Army soldier who acquired epidemic infectious hepatitis in Sicily in September, 1943. This virus, in feces or serum, produced the disease in human volunteers (Havens) inoculated orally or parenterally after incubation periods of fifteen to thirty-four days. As the characteristics of the disease associated with this virus correspond to the syndrome described as infectious hepatitis[1] and apparently are similar to those associated with virus I. H., Pa., the virus will be referred to herein as virus I. H., (S.). The material used in the present study, *feces pool* 1, *FIH*, (*S.*), consisted of pooled feces specimens obtained from volunteers with hepatitis due to oral inoculation with this virus by Dr. Havens.

B. *Dosage of Infectious Materials.* As the hepatitis viruses cannot as yet be isolated in pure form, the quantity administered can be estimated only in terms of the quantity of material used. In some of the various experiments reported herein, the dosages have not been listed as the quantities used were known to be infective from results of other experiments previously reported or from the results in control subjects reported herein. In the experiments on the effect of route of entry on the incidence of hepatitis, comparable doses were given by the parenteral and oral routes. Specific mention of dosage will be made in those experiments in which the dosage may have influenced the results obtained.

C. *General Procedure.* The general conduct of the transmission experiments in humans has been detailed in previous reports.[1,2,4,6,7,8] The term "*normal*" will be used herein to refer to volunteers who had no past history of recognized hepatic disease, no present history, physical signs or laboratory evidences of existing hepatic disturbance, and who had no previous inoculations with infectious materials. Subjects under thirty-five years of age were selected. A group of hepatic studies was carried out two or more times weekly before and after their inoculation with infectious, or potentially infectious, materials. The hepatic studies included the total and prompt direct-reacting serum bilirubin determinations, urine bilirubin and urobilinogen studies, cephalin cholesterol flocculation, thymol, and colloidal gold tests, total serum protein, albumin and globulin determinations, total and esterified serum cholesterol analyses and the bromsulphalein test.[5,8] Clinical and laboratory observations were continued for at least six months after inoculation irrespective of whether or not the subjects developed hepatitis. Volunteers who were inoculated with materials related to virus I. H., Pa., or I. H., S., were isolated for two to four months after the date of inoculation. Volunteers inoculated with materials related to virus SH were not isolated. All syringes and needles used in these studies were carefully cleaned and autoclaved for fifteen to thirty minutes after each use. Control subjects living under the same conditions as those inoculated were observed and sub-

jected to hepatic tests in connection with all of the experiments.

D. *Time Relationships in Immunity Studies.* The interval of time between an immunizing infection and the challenge inoculation used to test for the presence of immunity is of importance in the evaluation of the results. The length of this interval depends on whether it is measured from the time of onset, recovery, or from some other stage of the immunizing infection. In respect to hepatitis, the time at which antibodies begin to appear cannot as yet be determined. It is probable, however, that they are present long before recovery from hepatitis is complete. Furthermore, the time of recovery often is difficult to determine, as objective clinical evidences may disappear while laboratory evidence of hepatic disturbance persists or clinical manifestations may persist after the subsidence of laboratory evidence of hepatic disturbance. For these reasons, the interval between the immunizing infection and the challenge inoculation was measured from the time the diagnosis of hepatitis (initial immunizing infection) was definitely established to the time of the challenge inoculation.

E. *Diagnosis.* The diagnosis of *hepatitis with jaundice* was made in volunteers who developed the typical clinical and laboratory manifestations of the disease associated with visible jaundice and with a total serum bilirubin concentration higher than 2.0 mg. per 100 ml. The diagnosis of *hepatitis with subclinical jaundice* was made in those with typical symptoms and signs of hepatitis associated with a significant increase in the total serum bilirubin concentration above the preinoculation level for that volunteer and above the upper limit of the normal range (1.4 mg. per 100 ml.) but not exceeding 2.0 mg. per 100 ml. The *diagnosis of hepatitis without jaundice* was made in those who developed, after the usual incubation period, symptoms and signs suggestive of hepatitis and definitely significant laboratory evidences of hepatic disturbance but without elevation of the total serum bilirubin concentration above the upper limit of normal (1.4 mg. per 100 ml.). In such cases, an elevation of the total serum bilirubin concentration above the preinoculation range for the person concerned but not above the upper limit of the normal range (1.4 mg.) frequently was noted. Only those cases in which the authors were confident of the diagnosis are included in this category and they are therefore listed as hepatitis in the results. The diagnosis of *questionable hepatitis* was made in those who developed questionably significant, mild abnormalities in the responses of one or more of the various hepatic tests and who had no symptoms or signs suggestive of hepatitis. In such cases, the findings possibly could have been due to a very mild hepatitis but also probably could be explained by other non-specific disturbances. Cases falling in this group are mentioned in the results but are not listed as hepatitis. In none of the cases were the manifestations clinically significant or sufficient to interfere with routine duties.

STUDIES ON VIRUS S. H. (TABLE I)

1. *Effect of Route of Entry of Virus SH.* (a) *Parenteral route:* Twenty-five normal volunteers have been injected parenterally with virus SH (in plasma A). Of these, eighteen (72 per cent) developed acute hepatitis after two to four and one-half months, the disease being associated with visible jaundice in fourteen (78 per cent) and with subclinical jaundice in four (22 per cent). One additional person showed slight abnormalities in the results of the hepatic laboratory tests but these were not considered sufficient to warrant a diagnosis of hepatitis. Parenteral doses of 1, 2, 5, 9, 10, 12 and 250 cc. of plasma A induced hepatitis. The 2 cc. parenteral dose was

used most commonly. The twenty-five men were inoculated in groups of three to five men between October, 1943, and November, 1945. As no difference in incidence or severity of the disease was observed in the groups inoculated at different times, it laboratory evidence suggestive of hepatic disturbance. Virus SH (plasma A, 4 cc.) also was administered orally to four volunteers who, during the preceding six months, had recovered from an induced attack of infectious hepatitis due to virus I. H., (Pa.).

TABLE 1*

Material	Volunteers		Route	Results			
	Status	No.		No Hepatitis	Questionable Hepatitis	Definite Hepatitis	
						No.	Per Cent
Plasma A	Normal	25	Parenteral	6	1	18	72
		10	Oral	10	0	0	0
	Previous I.H.	4	Parenteral	2	0	2	50
		4	Oral	4	0	0	0
	Previous S.H.	9	Parenteral	4	5	0	0
Feces pools 1, 2, and 3 F.S.H	Normal	19	Oral	19	0	0	0
Seitz filtrate feces pool 2–3 F.S.H	Normal	5	Parenteral	4	1	0	0
Nasopharyngeal washing pool 1 N.P.S.H.	Normal	4	Nasopharynx and oral	4	0	0	0
Urine pool 1 U.S.H	Normal	1	Oral	1	0	0	0

* Results of transmission experiments with materials containing or related to virus SH. Volunteers designated "previous I.H." had had infectious hepatitis due to virus I. H., Pa. prior to inoculation with virus SH. Those designated "previous S.H." had had homologous serum hepatitis due to virus SH prior to reinoculation with virus SH.

appears that the virus retained its original activity after three and one-half years of residence in frozen plasma. The results in this group have been used, in the interpretation of the results of other experiments to be described, as an index of the expected incidence of hepatitis (72 per cent) in normal volunteers of this age group following parenteral injection of this agent. (b) *Oral route:* Virus SH (in 4 to 10 cc. doses of plasma A) was administered orally to ten apparently normal volunteers. During the subsequent period of observation (six to twelve months), none developed clinical or None of these men developed clinical or laboratory evidences of hepatic disturbance during a six-month period of observation.

The results show that virus SH was highly effective in producing obvious hepatitis when it was injected parenterally. In contrast, it was relatively ineffective when entry was by the oral-intestinal route, no signs of active infection being detected. Not including the negative results in the four men who previously had had infectious hepatitis, the difference in incidence of active hepatitis with the parenteral and oral routes of entry is statistically significant,

the probability of the difference occurring as a result of chance being once in 2,000 trials (Chi square = 12.08). The results also suggest that a previous infection with virus I. H., Pa. did not increase the susceptibility to orally administered virus SH. This observation is of interest because of the results of a previous study[1] suggesting that a previous attack of hepatitis due to virus SH was followed by greater than normal susceptibility to parenterally injected virus I. H., (Pa.).

2. *Presence of Virus SH in Human Biological Materials.* The results described above show that virus SH may be present in the blood. Attempts to demonstrate this virus in the feces of patients with hepatitis due to this agent have been described previously in part.[4] *Feces pools* 1, 2, *or* 3 *FSH* were administered *orally* to nineteen apparently normal subjects[4] and subsequently, the *Seitz filtrate*, obtained from a mixture of feces pools 2 and 3 FSH, was injected parenterally into five apparently normal subjects. None of those receiving the feces preparations orally or parenterally developed clinical or laboratory evidences of hepatitis during a six-month period of observation. One of the five injected parenterally showed slight abnormalities of uncertain significance in the results of certain hepatic tests but these alone were not sufficient to be regarded as adequate evidence of hepatitis and they were not supported by recognizable clinical manifestations.

In view of the failure of plasma A, which was known to contain virus SH, to induce apparent hepatitis when administered orally, the failure of feces from patients with hepatitis due to virus SH to induce apparent infection when administered orally provides no evidence concerning the presence or absence of the virus in the feces. The negative results thus could be explained either by an absence of the virus in the feces or, if present, by the relative ineffectiveness of the virus when administered orally. However, the negative results on subjects inoculated parenterally with the Seitz filtrate from the feces pools strongly suggest that the virus was not present in the feces preparations used herein, at least not in quantities sufficient to be detected by this method of testing. The results thus provide considerable evidence that virus SH was not present in detectable amounts in the feces of patients with active hepatitis due to parenterally injected virus SH.

The attempts to demonstrate virus SH in the nasopharyngeal washings and urine of patients with active hepatitis due to this virus have been too limited to warrant any conclusions. It has seemed desirable, however, to record (briefly) the results obtained to date. Nasopharyngeal washings pool 1 NPSH (see materials), after thawing, was sprayed into the nose and throat of each of four volunteers. A total of 4 to 5 cc. was administered, the material accumulating in the pharynx being swallowed. None of these men developed significant evidence of hepatitis during a six-month period of observation. Fifty cc. of *urine pool* 1 *USH* were given orally to the only volunteer available at the time. He showed no evidence of hepatitis during a ten-month period of observation. These results provide no conclusive evidence regarding the presence or absence of virus SH in the nasopharyngeal secretions and urine for the following reasons: (a) The pools did not include specimens from sufficient cases of this type of hepatitis; (b) the pools did not include specimens obtained during the earliest stages of the disease; (c) too few volunteers were available for an adequate test of the materials described; (d) even though a greater number of specimens representing all stages of the disease from a greater number of persons with this type of hepatitis had been tested, negative results would not have indicated an absence of

this virus in these materials since they were not tested by the parenteral route and the studies described above have indicated that this agent may not be effective by the oral-intestinal route. Thus no conclusions can be drawn from these studies with nasopharyngeal washings and urine obtained from patients with hepatitis due to virus SH.

3. *Characteristics of Hepatitis Induced by Parenterally Injected Virus SH.* The date of onset of hepatitis induced by this virus frequently was difficult to determine. In some cases, transient episodes characterized by mild symptoms and laboratory evidence of mild hepatic disturbance occurred prior to onset of clinically recognizable acute hepatitis. The onset of acute hepatitis leading up to the development of jaundice often was insidious and the initial symptoms often were so mild that their significance might have been overlooked had they not been associated with laboratory evidence of significant and progressively increasing hepatic disturbance. In some cases, laboratory evidence of hepatic disturbance was obtained before the onset of symptoms. None of the eighteen cases had elevations of temperature exceeding 100°F. (oral) at the onset. For these reasons it often was difficult to determine the exact incubation period, the day of onset frequently being indistinct. Thus it has seemed preferable in referring to the interval between inoculation and the occurrence of hepatitis to use the interval between inoculation and the development of jaundice (first significant elevation of serum bilirubin). Using this criterion, the interval from inoculation to jaundice in the eighteen cases of hepatitis due to parenteral injection of virus SH varied from two to four and one-half months. This interval apparently was not significantly influenced by the various doses of virus SH (in plasma) used in these studies.

4. *Resistance to Reinfection with Virus SH (Homologous Immunity) Following Recovery from Previous Infection with This Virus.* Nine volunteers who had recovered from hepatitis induced by parenteral injection of virus SH subsequently were reinoculated parenterally with this virus. The results have been reported in part in a preliminary report.[1] In respect to the severity of the first attack, three had overt jaundice of moderate degree, two had overt jaundice of mild degree, two had subclinical jaundice with symptoms of moderate degree, and two had very transient subclinical jaundice with only mild symptoms. The interval in months from the initial attack of hepatitis to the challenge inoculation of the nine volunteers was two and three-fourths, four and one-fourth, four and one-fourth, five and three-fourths, five and three-fourths, five and three-fourths, eight, nine and three-fourths and eleven and three-fourths months, respectively. Following the challenge inoculation, none of the nine volunteers developed incapacitating symptoms or jaundice although five[1] showed transient mild symptoms and/or laboratory findings suggestive of mild hepatic disturbance after one and one-half, two, two, three and four and one-half months, respectively. Although the findings in these five cases were suggestive of mild hepatic disturbance presumably related to the challenge inoculation with virus SH, the manifestations were not sufficient to interfere with the usual activities of the men and a diagnosis of hepatitis could not be established with certainty. None of the other four men (challenge inoculations with virus SH received after intervals of two and three-fourths, eight, nine and three-fourths, and eleven and three-fourths months) showed any manifestations, clinical or laboratory, suggestive of hepatitis. Thus clinically significant hepatitis was not observed in any of the nine men following a second parenteral inoculation with virus SH. As the expected

incidence of clinically significant hepatitis in apparently normal volunteers inoculated parenterally with virus SH for the first time is 72 per cent, the failure of any of the nine men tested to develop clinically significant hepatitis or jaundice provides strong evidence that the previous infection with virus SH was followed by complete, or nearly complete, resistance to the same virus for the periods of time involved in this investigation.

STUDIES ON VIRUS I. H., PA. TABLE II

1. *Effect of Route of Entry.* (a) *Oral route—Feces pool* 1 *FIH* has been administered orally to thirty-three apparently normal volunteers. Twenty-four (73 per cent) developed typical infectious hepatitis, the interval from inoculation to onset ranging from seventeen to twenty-seven days. Twenty-two (91 per cent) of the twenty-four cases of hepatitis developed overt jaundice, and two had hepatitis without jaundice. Another developed suggestive symptoms and signs but had no laboratory findings to support a diagnosis of definite hepatitis. The *Seitz filtrate of feces pool* 1 *FIH* was administered orally to three volunteers and all three (100 per cent) developed typical infectious hepatitis with jaundice,

TABLE II*

Material	Volunteers		Route	Results			
	Status	No.		No Hepatitis	Questionable Hepatitis	Definite Hepatitis	
						No.	Per Cent
Feces pool 1 F.I.H.	Normal	33	Oral	8	1	24	73
	Previous S.H.	1	Oral	0	0	1	100
	Previous I.H.	12	Oral	11	1	0	0
Seitz filtrate feces pool 1 F.I.H.	Normal	3	Oral	0	0	3	100
		3	Parenteral	3	0	0	0
Serum pool 2 S.I.H.	Normal	3	Oral	1	0	2	66
		6	Parenteral	4	1	1	16
	Previous S.H.	4	Parenteral	0	1	3	75
Serum pool 1 S.I.H.	Normal	3	Parenteral	3	0	0	0
Feces pool 3 F.I.H.	Normal	7	Oral	7	0	0	0
Feces pool 7–8 F.I.H.	Normal	5	Oral	3	2	0	0
Nasopharyngeal washings pools 1 and 2 N.P.I.H.	Normal	8	Nasopharynx and oral	8	0	0	0
Urine pool 1 U.I.H.	Normal	7	Oral	7	0	0	0

* Results of transmission experiments with materials containing or related to virus I. H., (Pa.). See legend of Table 1 for explanation of volunteers designated "previous S.H." and "previous I.H."

the onset occurring after intervals of twenty-eight, thirty, and thirty-two days, respectively.[5] *Serum pool* 2 *SIH* was given orally to three volunteers and, after intervals of twenty-six and thirty-three days, respectively, two (66 per cent) developed typical infectious hepatitis with jaundice.[5]

The results show that feces pool 1 FIH, the Seitz filtrate obtained from it, and serum pool 2 SIH contained virus I. H., Pa. and that the agent was filtrable. Combining the 3 groups, a total of thirty-nine men have received this virus orally. Twenty-nine (74 per cent) developed unquestionable infectious hepatitis, the interval from inoculation to onset ranging from seventeen to thirty-three days. The expected incidence of hepatitis in apparently normal persons of this age group following oral inoculation with virus I. H., Pa. thus would be in the neighborhood of 74 per cent (minimum 66 per cent).

The subjects receiving feces pool 1 FIH, the Seitz filtrate, and serum pool 2 SIH were inoculated in groups of three to six men over an interval of fourteen months. During this time the materials were stored in the frozen state at approximately minus 20°c. No apparent difference was observed in the incidence or severity of the disease in groups inoculated soon after collection of the materials as compared with those inoculated after storage of the material in the frozen state for periods up to fourteen months. Thus virus I. H., Pa. apparently retained its activity in spite of residence for at least fourteen months in the frozen feces preparations.

The studies concerning feces pool 1 FIH cited above and certain others reported elsewhere or as yet unpublished suggest some relationship between the quantity administered orally and the incubation period of the disease. In experiments involving different doses of feces pool 1 FIH (virus I. H., Pa.), the results have suggested that a decrease of the quantity administered orally below a certain critical level (less than 1.8 cc. of feces pool 1 FIH) resulted in a prolongation of the incubation period up to thirty-seven days.[5] (*b*) *Parenteral route:* The bacteriologically sterile *Seitz filtrate of feces pool* 1 *FIH* (1 cc.) was injected subcutaneously into three apparently normal volunteers. None developed clinical or laboratory evidences of hepatitis during a six-month period of observation. *Serum pool* 2 *SIH* (2.1 to 3 cc.) was injected parenterally into six apparently normal volunteers. After an interval of thirty-five days, one developed infectious hepatitis with subclinical jaundice (maximum total serum bilirubin concentration 1.8 mg. per 100 cc.). Sometime between the thirty-seventh and fifty-second day, another developed weakly positive thymol flocculation and colloidal gold tests but he had no symptoms or physical signs suggestive of any illness at any time and multiple other hepatic tests revealed no laboratory evidences suggestive of hepatic disturbance. If this represented a very mild infection, it apparently was not of clinical significance as he continued his usual physical activities, including moderately strenuous work and exercise, throughout the post-inoculation period. The other four showed no clinical or laboratory evidence of hepatitis during a six-month period of observation.

Thus, of nine apparently normal men inoculated parenterally with materials known to contain virus I. H., Pa., only one developed definite hepatitis and another may have had a subclinical infection. Using unquestionable hepatitis as the criterion, the incidence of hepatitis in this group of apparently normal persons inoculated parenterally with virus I. H., Pa. was eleven per cent and this one case was relatively mild. As the minimum incidence following oral administration of the same infectious materials (Seitz filtrate pool 1 FIH, serum pool

2 SIH) to apparently normal persons was 66 per cent, it appears that this virus was considerably more effective in inducing hepatitis in normal persons when entry was by the oral-intestinal route.

In addition to the nine men who received parenterally the materials known to contain virus I. H., Pa., three other volunteers were injected parenterally with serum pool 1 SIH.[5] None of the three volunteers developed clinical or laboratory evidences of hepatitis during a six-month period of observation. Unfortunately, volunteers were not available for a test of this material by the oral route so that the presence of the virus in this serum pool was not definitely established. As described in a previous report,[5] this pool consisted of portions of eight serum specimens collected from six patients during the first week and from two patients during the second week of hepatitis due to virus I. H., (Pa.). Based on previous experience and that of others,[5,9] the virus should have been present in this pool. However, the significance of the negative results of the parenteral inoculations with this material (pool 1 SIH) is uncertain due to the lack of definite evidence that the virus was present.

In view of the apparent relative resistance of normal persons to parenterally injected virus I. H., Pa., it is of particular interest that three of four men who had recovered from hepatitis due to virus SH (and then had shown resistance to reinfection with virus SH) developed hepatitis twenty-eight, twenty-eight and thirty-seven days, respectively, after *parenteral* inoculation with virus I. H., Pa. (serum pool 2 SIH, 2 cc.). The fourth man also developed similar symptoms and signs starting on the thirty-fifth day but the only significant laboratory evidence of hepatitis was the development, and persistence for one month, of a 4+ cephalin cholesterol flocculation test. It appears probable that these manifestations also were due to mild hepatitis. The incidence in this group thus was 75 to 100 per cent depending on the interpretation of the fourth case.[1] The severity of the disease in these three (or four) cases was mild. One developed overt jaundice (maximum total serum bilirubin, 4.0 mg. per 100 ml.), two developed subclinical jaundice, and the fourth (questionable case) had no jaundice. That the mildness of the disease probably was not due to a protective effect from the previous virus SH infection is suggested by the apparent greater susceptibility of these men, as a group, than normal persons to parenterally injected virus I. H., Pa. Furthermore, the severity of the disease in the one normal person who developed hepatitis after parenteral injection of this virus also was mild (maximum total serum bilirubin 1.8 mg. per 100 ml.). The results of this study thus showed that: (1) Persons previously infected with virus SH apparently were more susceptible as a group to parenterally injected virus I. H., Pa. than apparently normal persons; (2) Previous infection with virus SH did not protect against infection with virus I. H., Pa.; (3) in the four (or five) persons who developed hepatitis after parenteral injection of virus I. H., Pa., the interval between inoculation and onset did not exceed thirty-seven days.

2. *Presence of Virus I. H., Pa. in Human Biological Materials.* Pools of serum, feces, urine and nasopharyngeal washings obtained from patients with hepatitis due to virus I. H., Pa. (oral-intestinal route of entry) have been tested for the presence of the agent as measured by their effects in apparently normal human volunteers. As described herein and in a previous report,[5] serum (pool 2 SIH) and feces (pool 1 FIH) obtained during the active stages of the disease contained the virus whereas urine (pool 1 UIH) and nasopharyngeal washings (pools 1 and 2 NPIH) administered by the oral-intestinal route failed to induce the disease, suggesting that the virus was not

present in these materials, at least in quantities demonstrable by tests in volunteers.

In a preliminary study concerning the duration of the intestinal carrier state reported elsewhere,[4] single specimens of feces obtained from two volunteers approximately three weeks (thirty-third and forty-third day of disease, respectively) after the disappearance of jaundice due to orally administered virus I. H., Pa. were pooled and the pool (3 FIH) was administered orally to seven volunteers. None developed any evidences of hepatitis during a six-month period of observation suggesting that the virus was not present in these specimens.

At the present time, pools of feces and serum specimens obtained at frequent intervals between the third and tenth months of the disease from three volunteers with active chronic non-icteric hepatitis following acute hepatitis induced by orally administered virus I. H., Pa. are being tested for the presence of the agent. The pooled serum and feces preparations from these cases were administered to separate groups consisting of five apparently normal volunteers. During the seventy days which have elapsed to date, no definite evidences of hepatitis have been detected. The details and final results of this study will be reported later.

As feces specimens obtained from patients with hepatitis due to parenterally injected virus SH apparently did not contain the virus, it seemed important to determine if the feces of patients with hepatitis due to parenterally injected virus I. H., Pa. contained this virus. For this reason, feces pool 7–8 FIH (consisting of specimens obtained at frequent intervals from four volunteers during the early stages of hepatitis induced by parenteral injection of virus I. H., Pa.) was administered *orally* to five apparently normal volunteers. During the subsequent six-month period of observation, none of the five developed a clinically apparent attack of hepatitis or jaundice. Two of the five, however, presented laboratory evidences suggestive of mild hepatic disturbance starting after thirty days and persisting intermittently for approximately six weeks. The laboratory findings consisted of positive cephalin cholesterol flocculation tests (3 to 4+), weakly positive thymol tests and intermittent urobilinogenuria. Because of the timing and as no other cause was apparent, it seems probable that these manifestations were due to mild subclinical hepatitis. However, the results of this study must be regarded as inconclusive.

3. *Characteristics of Hepatitis Induced by Virus I. H., Pa.* In contrast to the onset of hepatitis due to virus SH, the onset of hepatitis due to virus I. H., Pa. usually was abrupt and suggestive of the onset of a generalized infection. There rarely was any difficulty in determining the day of onset of the disease. Symptoms and signs usually preceded significant laboratory evidence of hepatic disturbance by twenty-four to seventy-two hours. Fever was observed during the first days of the disease in thirty-three of thirty-four cases and in all of these, the temperature exceeded 100°F. (oral) at some time during the preicteric stage of the disease. This occurred irrespective of the route of inoculation (oral or parenteral). A febrile onset with the temperature exceeding 100°F. (oral) also was observed in four of five cases of hepatitis without overt jaundice due to this agent. One or more frank chills were not uncommon the first few days and chilly sensations were noted by nearly all of the patients. In the cases who received virus I. H., Pa. orally, the interval from inoculation to onset ranged from seventeen to thirty-three days and that from inoculation to jaundice ranged from twenty-two to thirty-seven days. In those who were injected parenterally with virus I. H., Pa., the interval from inoculation to onset ranged from twenty-eight to thirty-seven days. The interval from inoculation to jaundice in the

one of the five who developed overt jaundice was thirty-six days.

4. *Resistance to Reinfection with Virus I. H., Pa. Following Recovery from Previous Infection with This Virus.* Four volunteers who had recovered from infectious hepatitis with overt jaundice due to virus I. H., Pa. were challenged by *oral* inoculation with the same virus (in feces pool 1 FIH) five, seven and one-half, eight and nine months, respectively, after the onset of the previous attack of hepatitis. None of these men developed clinical or laboratory evidences of hepatitis during a six-month period of observation. Eight additional volunteers who had recovered from infectious hepatitis due to virus I. H., Pa., but who did not develop overt jaundice during the course of the disease, also were challenged by *oral* inoculation with the same virus (in feces pool 1 FIH) one, two, two, four, four and one-half, four and three-fourths, five and seven months after the onset of the previous attack of hepatitis. None of these men developed clinical manifestations or jaundice. Except for one man (challenged two months after the onset of the previous infection) who showed abnormal urobilinogenuria on the twenty-fourth and thirty-eighth days after the challenge inoculation, none showed evidence of hepatic disturbance detectable by the multiple tests used. Thus, none of twelve volunteers, challenged by oral inoculation with virus I. H., Pa. two to nine months after a previous infection due to the same agent, again developed significant evidence of hepatitis. As the incidence of hepatitis in normal groups of persons of this age group inoculated orally with virus I. H., Pa. (in feces pool 1 FIH) has averaged 74 per cent, these data provide significant evidence that an infection with virus I. H., Pa. was followed by resistance to reinfection by the same virus for at least the time periods covered in this experiment.

STUDIES OF HETEROLOGOUS IMMUNITY FOLLOWING INFECTIONS WITH VIRUSES S. H. AND I. H., PA. TABLE III

1. *Studies on Susceptibility to Virus I. H., Pa., Following Infection with Virus S. H.* These studies have been described in a previous report.[1] Five men resistant to parenterally injected virus SH, as demonstrated by challenge inoculation, were challenged (one orally, feces pool 1 FIH; four parenterally, serum pool 2 SIH) with virus I. H., (Pa.). Four of the five developed unquestionable acute hepatitis after intervals of twenty-five (oral inoculation), twenty-eight, twenty-eight and thirty-seven days. The fifth man, after thirty-five days, developed a mild illness associated with positive cephalin cholesterol flocculation tests which probably, but not unquestionably, also represented a mild type of hepatitis. Thus, these men with demonstrated resistance to reinfection with virus SH were not resistant to infection with virus I. H., (Pa.). In view of the previously cited evidence suggesting that normal volunteers were relatively resistant to parenterally injected virus I. H., Pa. (11 per cent incidence of very mild hepatitis), the occurrence of clinically significant hepatitis in three and possibly all of the four men of this group who were inoculated parenterally suggests that the previous infection with virus SH was followed by an increased, rather than a decreased, susceptibility to virus I. H., (Pa.). To summarize the results of this experiment, five men, following an infection with virus SH, first were found to have complete, or nearly complete, resistance to reinfection with virus SH and then were found to be susceptible to infection with virus I. H., (Pa.). The results apparently indicate that resistance against virus SH developed as a result of the first attack of hepatitis due to that virus. This afforded protection against reinfection

with the same agent, but did not afford protection against virus I. H., (Pa.).

Following recovery from the attack of hepatitis due to virus I. H., Pa., and five to eight months after the onset of that attack, four of the five men cited above again were challenged by oral inoculation with virus I. H., Pa. (feces pool 1 FIH). None of the four developed clinical or laboratory evidences of hepatitis during a six-month period of observation, and at the termination of the experiment, all appeared to be in good general condition without any clinical or laboratory findings suggestive of residual hepatic disturbance. Liver biopsies (surgical excision at laparotomy) were obtained from the four men, who had had four inoculations with infectious material and two attacks of hepatitis, just prior to the termination of the experiment. At the time of biopsy, no gross abnormalities in the size or appearance of the liver were apparent. The reports on the microscopic examinations of the biopsy specimens, which are not yet available but will be described in detail in a subsequent report, should provide interesting information concerning the completeness of recovery from multiple attacks of virus hepatitis.

2. *Studies on Susceptibility to Virus SH Following Infection with Virus I. H., Pa.* After apparently complete recovery from hepatitis due to virus I. H., Pa., and five to six months after the onset of that illness, four volunteers were challenged by parenteral inoculation with virus SH (in plasma A). Two of the four men developed hepatitis with jaundice, the interval from inoculation to jaundice being 101 and 102 days, respectively. As data cited above have shown that infection with virus I. H., Pa. is followed by resistance to reinfection with the same agent, the results suggest that infection with virus I. H., Pa. resulted in the development of resistance to reinfection by that virus but not to infection by virus SH.

TABLE III*

Volunteers		Challenge Inoculation		Results		
Status	No.	Virus	Route	No Hepatitis	Questionable Hepatitis	Definite Hepatitis
Previous infection with Virus S.H	9	S.H.	Parenteral	4	5	0
	5	I.H., Pa.	Parenteral or oral	0	1	4 (80%)
Previous infection with Virus I.H., Pa	12	I.H., Pa.	Oral	11	1	0
	5	I.H., S.	Oral	5	0	0
	4	S.H.	Parenteral	2	0	2 (50%)
Previous parenteral inoculation with Virus I.H., Pa., without subsequent apparent infection	9	I.H., Pa.	Oral	9	0	0

* Results of studies pertaining to homologous and heterologous immunity following apparent or possible inapparent infections with viruses SH and I. H., (Pa.). Expected average incidence of hepatitis in normal persons (no previous inoculations or history of hepatitis) of this age group inoculated with these viruses for the first time were as follows: Virus SH parenteral, 72 per cent; Virus I. H., Pa. oral, 74 per cent, parenteral, 11 per cent; Virus I. H., S. oral, 50 per cent on basis of small control group.

The data indicating that resistance produced by, and affording protection against, virus SH did not protect against virus I. H., Pa., and that resistance produced by, and affording protection against, virus I. H., Pa., did not protect against virus SH provide strong evidence of an antigenic difference in the two viruses. These observations indicate that at least two viruses, which may be different viruses or only different strains of the same virus, are concerned in the problem of virus hepatitis.

3. *Resistance to Virus I. H., S., Following Infection with Virus I. H., Pa.* In view of the apparent antigenic difference between virus SH and virus I. H., Pa., it appeared desirable to investigate the antigenic relationship between the infectious hepatitis virus obtained in Pennsylvania (virus I. H., Pa.) and that obtained from a patient who acquired infectious hepatitis in Sicily (virus I. H., S.). Four men who apparently had completely recovered from hepatitis due to virus I. H., Pa., and one who had failed to develop hepatitis after oral inoculation with this virus (feces pool 1 FIH) were inoculated orally with feces pool I. H., S., five and one-half to eight months after the onset of the attack of hepatitis caused by virus I. H., (Pa.). None of these five men developed clinical or laboratory evidences of hepatitis during a six-month period of observation. One (50 per cent) of the only two normal volunteers available at the time as controls for this experiment developed acute hepatitis twenty-five days after oral inoculation with feces pool I. H., (S.). The second volunteer showed laboratory findings suggestive of mild hepatic disturbance starting twenty-eight days after inoculation, but these were not sufficient to warrant a definite diagnosis of hepatitis. Although the groups are too small for the results to be of definite significance, they suggest that the previous infection with virus I. H., Pa. produced antibodies that were effective in protecting against virus I. H., (S.). This in turn suggests an antigenic similarity in viruses I. H., Pa. obtained in Pennsylvania and virus I. H., S. obtained in Sicily.

4. *Observations Bearing on the Relationship between the Virus Responsible for So-called "Catarrhal Jaundice" and Viruses I. H., Pa. and SH.* Although there appears to be no basis for differentiation between so-called "catarrhal jaundice" and infectious hepatitis, the following observations are of interest: (*a*) F.D.W.L. developed a disease in 1932 that was diagnosed as "catarrhal jaundice" by Dr. T. Grier Miller, Clinical Professor of Medicine at the School of Medicine of the University of Pennsylvania. In 1942, during an attack of mumps, he received an intravenous infusion of 250 cc. of plasma A (before this plasma was known to contain virus SH). Seventy-six days later he developed acute hepatitis associated with intense jaundice that persisted for three months.[3] This series of events showed that an attack of "catarrhal jaundice" did not result in immunity effective against virus SH ten years later. (*b*) Volunteer H. J. C. developed in 1939, while a student at Yale University, a disease that was diagnosed as "catarrhal jaundice." In 1943, he was injected parenterally with virus SH and after sixty-seven days developed acute hepatitis. Subsequently, after recovery, he was reinoculated parenterally with virus SH and developed no definite indications of hepatitis during a six-month observation period. During the following year he received two inoculations (six months apart) with virus I. H., Pa., one parenteral and one oral. He showed no signs of hepatitis following either of these inoculations. Of particular interest is the fact that he was the only one of a group of six men subjected to the same series of four inoculations (two with virus SH, two with virus I. H., Pa.) who failed to develop hepatitis as a result of the first inoculation (third of the series) with virus

I. H., (Pa.). He also was the only one of the six men who, previous to participation in these experiments, had had a recognizable attack of hepatitis ("catarrhal jaundice" in 1939). This series of events suggests that he may have been protected from virus I. H., Pa. as a result of immunity acquired from the previous "catarrhal jaundice" rather than as a result of the previous infection with virus SH. The results also show that an attack of "catarrhal jaundice" did not produce immunity effective against virus SH injected parenterally four years later but may have produced immunity effective against virus I. H., Pa. five years later. (*c*) Subject M. W. reported an attack of jaundice in childhood at the age of six (1927) that was diagnosed as "catarrhal jaundice." In 1945, at six-month intervals, he received two inoculations with virus I. H., Pa. orally. He did not develop significant clinical manifestations or other definite evidence of acute hepatitis as a result of either inoculation. This series of events suggest that his resistance to virus I. H., Pa. may have been due to immunity acquired as a result of the attack of "catarrhal jaundice" eighteen years earlier.

These cases show that two persons were not resistant to virus SH four and ten years after so-called "catarrhal jaundice." They also show that two persons apparently were resistant to virus I. H., Pa. five and eighteen years after an attack of "catarrhal jaundice." The observations suggest an antigenic similarity of the causative agent of so-called "catarrhal jaundice" and virus I. H., (Pa.). This is not unlikely as there is no available evidence of a difference in the two diseases. On the other hand, the findings suggest a difference in the antigenic properties of the causative agent of "catarrhal jaundice" and virus SH. In view of the evidence cited herein of an antigenic difference in viruses I. H., Pa. and virus SH, an antigenic difference between the virus of "catarrhal jaundice" and that of virus SH would be expected as the former probably is the same or closely related to virus I. H., (Pa.).

STUDIES RELATING TO POSSIBILITIES OF ACTIVE IMMUNIZATION AGAINST VIRUS I. H., PA.

In this study, advantage was taken of the apparent resistance of normal persons to parenterally injected virus I. H., Pa. and their marked susceptibility to this virus administered by the oral route. Nine men who failed to develop clinical or laboratory evi-

TABLE IV*

Observation	Virus I. H., Pa.	Virus S. H.
1. Type of onset of hepatitis	Abrupt and usually with fever exceeding 100°F. (oral)	Comparatively insidious and usually afebrile or with fever not exceeding 100°F.
2. Interval from inoculation to onset of acute hepatitis	17 to 37 days	2 to 4½ months
3. Incidence of hepatitis in normal volunteers following oral inoculation	High	0
4. Incidence of hepatitis in normal volunteers following parenteral inoculation	Low	High
5. Presence of agent in feces	+	−
6. Resistance to infection after previous infection with virus I. H., Pa.	+	−
7. Resistance to infection after previous infection with virus S. H.	−	+

* Summary of results with Viruses I. H., Pa. and SH indicating that they are not identical viruses and affording satisfactory evidence of the existence of at least two different strains or types of hepatitis viruses.

dences of active infection following parenteral injection of virus IH (three with the Seitz filtrate of feces pool 1 FIH, three with serum pool 2 SIH, and three with serum pool 1 FIH) were inoculated *orally* with feces pool 1 FIH six to thirteen months after the previous parenteral injection. These men had no previous history of recognizable hepatitis. None of the nine men developed clinical or laboratory evidences of hepatitis during the six-month period of observation following their oral inoculation with feces pool 1 FIH. As hepatitis would be expected to occur in approximately 74 per cent of normal persons of this age group inoculated orally with this material, the failure of any of these nine men to develop evidences of active infection strongly suggests that they had been immunized by their previous parenteral inoculations which had produced no signs of active infection. Supporting this possibility is the evidence of acquired immunity provided by the negative results following challenge inoculations with orally administered virus I. H., Pa. (in feces pool 1 FIH) of the eight volunteers who previously had had very mild hepatitis without jaundice due to virus I. H., Pa.

Although these studies provide no information of the total duration of such acquired immunity, these observations suggesting that active immunization may be possible appear to be of considerable importance. They also provide evidence that the decreased susceptibility of the general population over thirty-five years of age to infectious hepatitis may be due, at least in part, to immunity acquired as a result of inapparent or subclinical infections. This is of interest in connection with the apparent presence of antibodies in human immune serum globulin prepared from large pools of normal human adult plasma which have been shown to be effective in protecting against virus I. H., Pa. and other strains of infectious hepatitis virus.[10,11,12]

COMMENTS

At the time of initiation of our studies on virus hepatitis in 1943, the authors were inclined to share the opinion of many that the etiological agents responsible for infectious hepatitis and homologous serum hepatitis probably were the same and that the differences noted in respect to incubation period, type of onset and frequency of secondary cases possibly were due to a difference in the route of entry. The results of studies reported herein have indicated, however, certain differences which appear to be incompatible with the concept of the existence of only one strain of hepatitis virus. The differences apparent from the results obtained to date in relation to the two viruses studied (virus SH and virus I. H., Pa.) are summarized in Table IV. These data, particularly the lack of cross immunity indicating an antigenic difference, justify the conclusion that virus SH and virus I. H., Pa. are not identical viruses and appear to establish the existence of at least two different strains or types of hepatitis virus.

Havens and his associates[9,13] have studied a strain of infectious hepatitis virus obtained in Sicily. The behavior of this virus in volunteers apparently has been almost identical with that of virus I. H., Pa. with one possible exception. The reported data of Havens and Paul et al. indicate that the Sicilian strain has been almost as effective in inducing hepatitis in apparently normal persons when injected parenterally as when administered orally in contrast to the low incidence of hepatitis in normal persons injected parenterally with virus I. H., (Pa.). Whether or not this is indicative of a difference in the two viruses is uncertain. The preliminary studies, reported herein, of the immunological relationships of these two strains of infectious hepatitis virus suggest that they are antigenically similar. It is of particular interest that parenteral injection

of either of these viruses has been associated with the incubation period characteristic of infectious hepatitis (not over thirty-seven days in studies reported to date). This provides strong evidence that the two to four and one-half month interval between the parenteral injection of some other hepatitis viruses and the appearance of jaundice or definite hepatitis is not just the result of the parenteral route of entry.

Havens[6] also has reported the finding of the Sicilian strain of infectious hepatitis in the feces of hepatitis patients who had acquired the disease as a result of parenteral injection of this agent. As previously stated, similar studies reported herein were inconclusive concerning the presence of virus I. H., Pa. in the feces of hepatitis patients who had acquired the disease following parenteral injection of this virus. However, the findings of Havens in this respect appear to be conclusive and constitute, as he points out, another apparent difference between infectious hepatitis and homologous serum hepatitis, the etiological agent not yet having been demonstrated in the feces of patients with the latter disease.[4] Paul, Havens, Sabin and Philip[13] also have studied a hepatitis virus obtained from the Middle East which apparently is similar to virus SH used in the present studies. This Middle East virus induced hepatitis in normal volunteers two to four and one-half months after parenteral injection. Volunteers recovered from hepatitis due to this virus again developed hepatitis twenty to twenty-five days after inoculation with the Sicilian strain of infectious hepatitis virus.[14] Their findings with these two viruses thus have been similar to those observed in connection with viruses I. H., Pa. and virus SH. As the results obtained by other investigators in their studies of various hepatitis agents have been reviewed in our previous reports[1,2,3] and in those of Havens,[9] further consideration of these data in the present report appears to be superfluous.

There is urgent need, however, for a reconsideration of some of the reported experimental data in view of the newer knowledge concerning methods of transmission and the apparent existence of two, and possibly more than two, types of hepatitis viruses. There is a general tendency to diagnose all cases of hepatitis who have not had injections of blood, plasma, serum or biologicals containing blood products, as infectious hepatitis. Undoubtedly, some cases of hepatitis due to agents similar to virus I. H., Pa. have been called homologous serum hepatitis and some cases due to agents similar to virus SH have been called infectious hepatitis. This is particularly apt to occur because both the virus of serum hepatitis and that of infectious hepatitis can be transmitted by blood, plasma or serum. Thus, if the term homologous serum hepatitis is to be used for any type of virus hepatitis in which the agent has been transmitted by parenteral introduction of blood or blood products, the two types described in connection with parenteral injection of virus I. H., Pa. (or virus I. H., S., Havens) and virus SH must be recognized. Furthermore, it has been suggested that these viruses may be transmitted by improperly sterilized syringes and needles used only for withdrawal of blood or for parenteral injections of materials of any type.[15] Such procedures, often performed on large groups of persons for prophylactic or diagnostic purposes, may be overlooked as sources of infection with the serum hepatitis virus and subsequent hepatitis developing in such persons thus regarded as a naturally acquired infectious hepatitis since no history of injection of a blood product may be obtained. Likewise a person may have been considered to have homologous serum hepatitis because of previous administration of a blood product which, however, may have con-

tained the virus of infectious hepatitis rather than that of serum hepatitis. These and other factors may account for some of the apparent inconsistencies in the behavior of various hepatitis viruses of supposedly similar or different origin reported by investigators in this field.

SUMMARY AND CONCLUSIONS

Some of the properties of hepatitis viruses obtained from three different immediate sources have been studied. Virus SH, present in a pool of plasma, induced hepatitis, after two to four and one-half months, in a high percentage (72 per cent) of normal volunteers inoculated parenterally but failed to induce the disease in any of ten normal volunteers who were inoculated orally. Feces obtained from volunteers with virus SH hepatitis failed to induce hepatitis when administered orally or parenterally (Seitz filtrate) to volunteers. In a preliminary study, nasopharyngeal washings and urine from volunteers with virus SH hepatitis also failed to induce the disease in volunteers to whom they were administered by the nasopharyngeal and oral routes but for reasons described, these studies do not warrant conclusions regarding the presence of the virus in these materials. Virus SH remained active after three and one-half years residence in frozen plasma. No consistent effect on the interval from inoculation with virus SH to the onset of hepatitis was noted with the different quantities injected parenterally. Compared to the type of onset of hepatitis due to virus I. H., Pa., the onset of hepatitis due to virus SH was relatively insidious and usually was not associated with elevations of temperature greater than 100°F. (oral). Following hepatitis due to virus SH, all volunteers tested were found to be resistant to reinfection with virus SH but were susceptible to infection with virus I. H., (Pa.).

Virus I. H., Pa., initially found in the feces of patients involved in an epidemic of hepatitis at a summer camp in Pennsylvania, induced active hepatitis, after seventeen to thirty-seven days, in a high percentage (73 per cent) of normal volunteers who were inoculated orally but in only one (11 per cent) of nine normal volunteers inoculated parenterally. In volunteers who had recovered from hepatitis due to virus SH, however, parenteral injection of virus I. H., Pa., in contrast to the results in normal persons, induced active hepatitis in three, (75 per cent) and possibly four, (100 per cent) of the four men so inoculated. Regardless of the route of inoculation (parenteral or oral), the interval from inoculation with virus I. H., Pa. to the onset of hepatitis did not exceed thirty-seven days and the onset was associated with elevation of temperature that exceeded 100°F. (oral) in all but one case. Virus I. H., Pa. was shown to be present in the blood and feces (including a Seitz filtrate obtained from a feces suspension) of patients with active hepatitis due to oral administration of this virus but apparently was not present, at least in sufficient quantities to infect volunteers, in the nasopharyngeal washing and urine pools tested. Virus I. H., Pa. apparently was not present, at least in quantities sufficient to infect volunteers, in single specimens of feces obtained from two persons three weeks after the disappearance of jaundice due to previous oral administration of this virus. Studies for the presence of virus I. H., Pa. in the feces of persons with hepatitis caused by parenteral inoculation with this virus were inconclusive. Two of the five volunteers inoculated orally had laboratory findings suggestive of mild hepatic disturbance but these findings alone were not considered sufficient to justify a definite diagnosis of hepatitis. The results with a relatively small range of orally administered doses of virus I. H., Pa. suggested that a decrease below a certain quantity (in terms of the amount of infective feces pool given) resulted in a prolongation

of the incubation period, although in no instance in the present studies was the incubation period longer than thirty-seven days. Following hepatitis due to virus I. H., Pa., all of the twelve volunteers tested were resistant to reinfection with this virus but two of four such volunteers were susceptible to parenterally injected virus SH as indicated by the occurrence of hepatitis with jaundice three months after inoculation. After recovery from infection with virus I. H., Pa., the five volunteers tested apparently were resistant to oral inoculation with virus I. H., S. (a strain of infectious hepatitis virus obtained in Sicily). Observations bearing on the relationship between the etiological agents responsible for so-called "catarrhal jaundice" and viruses SH and I. H., Pa. are briefly discussed. Studies suggesting that volunteers who failed to show signs of active infection following parenteral inoculation with virus I. H., Pa. were actively immunized by that inoculation are described. The significance of the results of some of the studies is briefly discussed, and possible explanations for apparent discrepancies in the results of different investigations are considered. It is concluded that the data presented constitute satisfactory evidence of the existence of at least two different strains or types of hepatitis viruses.

Acknowledgement. These investigations were made possible through the cooperation of the administrative staffs of Selective Service (Camp Operations Division), the National Service Board for Religious Objectors, the American Friends Service Committee, the New Jersey State Hospital (Trenton, New Jersey) and the Philadelphia State Hospital. We are particularly indebted to the members of the technical staffs of our laboratories in the Hospital of the University of Pennsylvania and in the New Jersey State Hospital, Trenton, N. J. The assistance of various members of the staffs of the Biochemical Laboratory of the Philadelphia General Hospital, the William Pepper Laboratory of Clinical Medicine of the Hospital of the University of Pennsylvania and the Laboratories of the New Jersey State Hospital in the conduct of certain phases of the studies is greatly appreciated. The advice and assistance of Dr. John G. Reinhold, Principal Biochemist of the Philadelphia General Hospital, who supervised the biochemical studies, were invaluable. Finally, the authors gratefully acknowledge the contribution made by the members of Civilian Public Service Unit No. 140, Philadelphia, Pennsylvania, who served as experimental subjects as well as assisting in the conduct of a large part of the technical work connected with the investigations.

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Susceptibility to Sulfadiazine of Hemolytic Streptococci Recovered in Army Camps*

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INTEREST in sulfonamide-resistant hemolytic streptococci has recently been stimulated by the appearance in the Navy of sulfonamide-resistant variants following programs of mass sulfonamide prophylaxis of respiratory disease.[1,2] Data are lacking, however, to indicate whether the resistant forms appeared during treatment of individuals who previously harbored only sensitive strains, or whether the resistant streptococci had already been present in the population, and were widely disseminated after sensitive strains had been suppressed. It is of importance in assessing the routine use of sulfonamides in treatment of hospitalized patients and ambulatory carriers to know whether sulfonamide-resistant streptococci frequently emerge during the treatment of individuals harboring sensitive strains. If this is a common occurrence, the use of sulfonamides should be avoided whenever possible. If not, their use in individual cases of streptococcal infection and their administration to carriers in special instances is often justifiable.

During a study of streptococcus carriers at Fort Lewis, Washington, and Fort Douglas, Utah, in 1945, the opportunity arose for measuring the resistance to sulfadiazine of strains recovered from ambulatory carriers and patients prior to the administration of this drug, and in many instances to test strains from the same individual after it was given. In the latter group, consisting of forty-five individuals harboring sulfonamide-sensitive streptococci, no resistant forms were found at the end of the period of treatment. These observations and certain others bearing upon the general problem are presented in this paper.

MATERIALS AND METHODS

Source of Streptococci. The streptococci were recovered from the nose and throat of hospitalized patient-carriers and ambulatory carriers among the military personnel of Fort Lewis, Washington, and from an A.S.T.P. unit at the University of Utah, Salt Lake City, whose personnel were hospitalized at Fort Douglas, Utah.

Identification of Streptococci. All the streptococci were grouped and typed by the method of Swift, Wilson and Lancefield.[3] Only Group A strains are reported in this paper.

Technic of Sulfonamide Resistance Tests. Sulfonamide resistance was expressed as the highest concentration of sulfadiazine permitting growth of a small inoculum (20 to 200 colonies) of hemolytic streptococci in eighteen to twenty-four hours. Two kinds of media were employed: (1) The semi-synthetic medium of Adams and Roe[4] as adapted in semi-solid form by Wilson,[5] en-

* From the Commission on Air-Borne Infections, Army Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, U. S. Army and the Department of Medicine, University of Chicago. The Commission wishes to acknowledge the cooperation of the many medical officers at Fort Lewis, Washington and Fort Douglas, Utah, whose support made these studies possible.

riched with 10 per cent rabbit serum, and (2) tryptose phosphate broth, Difco, enriched with 10 per cent horse serum. Though horse serum provided an adequate enrichment for tryptose phosphate broth, it was not a satisfactory supplement for the semi-synthetic medium. That some factor essential for growth of hemolytic streptococci in Adams-Roe medium was not present in the fresh serum of horses at Fort Lewis is surprising since Wilson[5] was able to utilize the serum of horses at Bethesda, Maryland, for this purpose, provided xanthine was added. The addition of xanthine did not replace the missing factor in the serum of horses at Fort Lewis. The factor was present in rabbit serum, however, which afforded a satisfactory enrichment for this medium.

The technic of Wilson, with slight modifications, was employed with both media. The unknown strain was grown for eighteen to twenty-four hours in the test medium free of sulfonamide. If a heavy growth was present the next morning, the culture was diluted to a standard density in a photoelectric colorimeter. One standard 3 mm. platinum loopful of the diluted culture was added to 2.5 cc. of the same broth (without serum enrichment) as a diluting fluid. The dilution tube was then shaken thirty times by hand. One standard 3 mm. platinum loopful was inoculated into a series of Wassermann tubes, the first containing medium free of sulfonamide, and the others containing sulfadiazine in two-fold or five-fold increasing concentrations.

The test was incubated eighteen to twenty-four hours at which time macroscopic growth was noted. Visual readings were made in both media. In the semi-solid Wilson medium, in which discrete colonies could be identified, the last tube containing any colonies was regarded as the end point. In the tryptose phosphate medium, turbidity was recorded as one, two, three or four plus. Usually end points at eighteen to twenty-four hours were sharp and clear, heavy macroscopic growth being seen in one tube and no growth at all in the next. Occasionally, however, end points were not distinct, and anomalous results sometimes occurred which could not be accounted for by different lots of medium or different samples of horse serum. The last tube giving a two plus reading was taken as the end point. Most of the strains which did not give clear cut results in the tryptose phosphate medium were later checked with the Wilson medium. In each day's tests, known sulfonamide sensitive and resistant strains were included as controls upon the batch of medium.

Definition of Sensitive and Resistant Strains. For purposes of discussion, strains are arbitrarily designated as sensitive, moderately resistant or highly resistant. They are referred to in these terms rather than in actual concentrations because some of the strains tested more than once grew in slightly different concentrations at different times and because some strains were tested in two-fold increasing concentrations of sulfadiazine (1.25, 2.5, 5, 10, 20, 40, 80, 160 mg. per cent), whereas later it was found just as satisfactory to employ five-fold increases (1, 5, 25, 125 mg. per cent). The arbitrary designations are:

HIGHEST CONCENTRATION SULFADIAZINE PERMITTING GROWTH

	In Wilson Semi-synthetic Medium, Mg. Per Cent	In Tryptose-phosphate Broth with 10 Per Cent Horse Serum, Mg. Per Cent
Sensitive	Control tube only or 1	Control tube only, 1, 1.25, 2.5 or 5
Moderately resistant	5	10, 20 or 25
Highly resistant	25 or 125	40, 80, 125 or 160

RESULTS

In Vitro Sensitivity of Strains Recovered from Patients and Ambulatory Carriers before the Administration of Sulfadiazine. Strains recovered at Fort Lewis are summarized in Table I. Sulfonamide-sensitive streptococci of various assorted types, including 3, 17 and 19 accounted for 86 per cent of the 107 strains tested. All but one of the highly resistant forms were Type 17, the one exception being Type 19. Most of these resistant streptococci came from patients who subsequently received sulfadiazine with no clinical or bacteriological benefit. One resistant Type 17 strain was dispersed in great numbers by a patient with scarlet fever, resulting in the cross infection of four nearby patients whose original infection was measles or else scarlet fever due to a different type. None of the five responded to sulfadiazine though they were all successfully treated with penicillin.

TABLE I
IN VITRO SENSITIVITY OF GROUP A STREPTOCOCCI RECOVERED FROM 76 UNTREATED CARRIERS AT FORT LEWIS

	No. of Strains	Per Cent	Types
Sensitive	92	86.0	1, 3, 6, 11, 12, 14, 17, 19, 24, 44, untypeable Group A
Moderately resistant	1	0.9	36
Highly resistant	14	13.1	17, 19
	107	100.0	

The origins of these strains were: nose 58; throat 45; ear 1; blankets 3.

Table II presents tests upon strains isolated at Fort Douglas. They were obtained from an epidemic of Type 19 infection, followed by a wave of Type 17 cases. After the Type 19 epidemic had passed its peak, the nasal carriers were treated with 1 Gm. of sulfadiazine a day, with rapid disappearance of streptococci from the noses of most of the carriers of Type 19 but not of the Type 17 organisms.[6] In fact, several successfully treated carriers of Type 19 streptococci became infected with Type 17 while still receiving sulfadiazine. One hundred per cent of the Type 19 strains were susceptible in vitro, whereas 94 per cent of the Type 17 strains were highly resistant.

TABLE II
IN VITRO SULFONAMIDE SENSITIVITY OF STREPTOCOCCI RECOVERED IN THE EPIDEMIC AT FORT DOUGLAS IN APRIL AND MAY, 1945

	Type 19		Type 17	
	No. of Strains	Per Cent	No. of Strains	Per Cent
Sensitive	97	100	2	6
Highly resistant	0	0	29	94

The 128 strains were obtained from eighty patients and ambulatory carriers. Nose and throat strains are about equally represented.

Failure of Sulfonamide-Resistant Streptococci to Appear in Forty-five Carriers Treated with Sulfadiazine. Sulfonamide-sensitive streptococci were recovered from the nose and/or throat of forty-five carriers before and after the administration of sulfadiazine. Of these, twenty-six were hospitalized patients who received 1 Gm. a day for four to ten days, six hospitalized patients treated with 3 to 6 Gm. a day for total doses of 12 to 51 Gm., and 13 were ambulatory carriers given 1 Gm. a day for eleven to fifty days. In most instances the streptococci disappeared from the nose or were greatly reduced in number during treatment, though they persisted in the throat in about half the cases. After the cessation of treatment, however, streptococci of the same serological type were again recovered from the noses of 95 per cent of the hospitalized patients and 23 per cent of the ambulatory carriers.[6] By testing the

strains recovered after treatment, it was possible to know whether resistant forms had developed.

TABLE III
IN VITRO SENSITIVITY TO SULFADIAZINE OF STREPTOCOCCI RECOVERED FROM FORTY-FIVE CARRIERS BEFORE AND AFTER TREATMENT—FORT LEWIS

	Per Cent of Strains Found to Be			No. of Strains
	Sensitive	Moderately Resistant	Highly Resistant	
Before treatment....	100	0	0	53
After treatment.....	100*	0*	0	76

* One strain of Type 19 streptococcus may have been slightly resistant after treatment. The number of strains from the nose and the throat were about equally divided. The type distribution among the forty-five carriers was: Type 1—13; Type 3—7; Type 12—6; Type 14—5; Type 17—1; Type 19—7; Type 24—1; Group A, not typeable —5.

The results are summarized in Table III. No resistant strains were encountered among the fifty-three tested before treatment or the seventy-six from the same individuals after treatment. The only suggestion of development of resistance was in one strain of Type 19 streptococcus which grew in 10 mg. per cent sulfadiazine in tryptose phosphate broth, a "borderline" concentration. Unfortunately, this test was not repeated.

The possibility that certain types, namely, 3, 17 and 19 might be more prone to develop resistance than other types cannot be ruled out. Only 33 per cent of this series belong to these three types.

Strains of Type 17 organisms growing in 125 mg. per cent sulfadiazine were recovered both before and after treatment from five patients.

Effect of Sulfadiazine upon Sulfonamide-Sensitive Streptococci in the Nose as Compared with the Throat. Table IV presents two cases which illustrate the bacteriostatic effect of sulfadiazine on streptococci present in the nose as compared with the throat. In Case I, streptococci were suppressed in both nose and throat during treatment. This was noted in 50 per cent of "successfully" treated carriers of sulfonamide-susceptible streptococci. In Case II, however, streptococci of the same serological type, the same sulfonamide-susceptibility in vitro, and presumably arising

TABLE IV
EFFECT OF SULFADIAZINE UPON SULFONAMIDE-SENSITIVE STREPTOCOCCI IN THE NOSE AS COMPARED WITH THE THROAT

Date	Throat Culture	Sulfonamide Sensitivity* of Throat Culture	Nose Culture	Sulfonamide Sensitivity* of Nose Culture	Sulfadiazine Gm. per day
Case I—Type 1					
1945					
Feb. 15....	+++	C	+++	2.5	0
Feb. 16....	+++	....	+++	....	0
Feb. 17....	+++	....	+++	....	1
Feb. 19....	0	....	+	....	1
Feb. 20....	0	....	+	....	1
Feb. 21....	+	....	0	....	1
Feb. 22....	0	....	0	....	1
Feb. 23....	0	....	0	....	0
Feb. 28....	+++	....	+	....	0
March 5...	+++	1.25	+	....	0
March 26..	+++	C	0	....	0
Case II—Type 12					
Feb. 2.....	+++	1.25	+++	2.5	0
Feb. 3.....	+++	....	+++	....	0
Feb. 4.....	+++	....	+++	....	1
Feb. 5.....	+++	....	+++	....	1
Feb. 6.....	+++	....	++	....	1
Feb. 7.....	+++	....	0	....	1
Feb. 8.....	+++	....	1 colony	....	1
Feb. 9.....	+++	....	0	....	0
Feb. 12....	+++	C	0	....	0
Feb. 15....	+++	2.5	+++	1.25	0
Feb. 20....	++	....	+++	....	0

* Sulfonamide sensitivity is expressed as the highest concentration of sulfadiazine permitting visible growth in the tryptose phosphate medium, as described under methods. C means that growth occurred only in the control tube. Nose and throat cultures are graded +, ++, or +++.

from the same original infecting strain, were suppressed in the nose during sulfadiazine treatment but persisted in the throat.

COMMENT

That sulfonamide-resistant streptococci were not found after treatment of forty-three carriers is perhaps not surprising. One can only conclude from this observation that the emergence of sulfonamide-resistant streptococci during the administration of small doses of sulfonamides is not common. One cannot, however, conclude that resistant forms do not appear when thousands of carriers are treated in this manner. It is hoped that data will be available from other groups larger than the ones we have studied.

Nor can definite statements be made about the origin of the sulfadiazine resistant Type 17 streptococci recovered from both military personnel and civilians under military supervision, none of whom had received sulfonamides. These strains were detected in 1945, many months after the appearance of resistant variants in a large Naval Station in the Northwest.[2] It is conceivable that streptococci from this Naval Station had spread to non-naval personnel in the same manner as they spread from the Naval Station in the northwest to those in the south and east.[2]

The more marked bacteriostatic effect of sulfadiazine upon sulfonamide susceptible streptococci present in the nose than upon the same bacteria in the throat emphasizes the importance of local factors in the action of sulfonamides in vivo. In this instance we do not know what these local factors were. The three possibilities which appear reasonable to us are: (1) The host's defense mechanism is more powerful in the nose than in the throat, as evidenced by the natural tendency in untreated carriers for the nose culture to clear faster than the throat culture; (2) a higher local concentration of sulfonamide in the nose than the throat; and (3) a higher concentration of sulfonamide antagonists in the throat than in the nose. These possibilities have not been explored.

SUMMARY

1. The administration of 1 Gm. of sulfadiazine a day to forty-five carriers of Group A hemolytic streptococci was not followed by the appearance of sulfonamide-resistant variants. The duration of treatment varied from four to fifty days.

2. Eighty-six per cent of 107 strains recovered from seventy-six untreated carriers of Types 1, 3, 6, 11, 12, 14, 17, 19, 24, 44 and untypeable Group A streptococci were susceptible to sulfadiazine in vitro. Thirteen per cent, all of these Type 17 except for one Type 19, were highly resistant.

3. The importance of local factors in influencing the bacteriostatic effect of sulfonamides in vivo was emphasized by the observation that the action of sulfadiazine upon sulfonamide-sensitive streptococci in the nose was more marked than upon sulfonamide-sensitive strains of the same serological type in the throat.

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The Effect of an Elevated Temperature on the Action of Penicillin on Viridans Streptococci

Isolated from Patients with Subacute Bacterial Endocarditis

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PREVIOUS studies[1] have shown that the rate at which viridans streptococci are killed *in vitro* by an amount of penicillin in excess of that necessary for bacteriostasis may differ widely for different strains. When the bactericidal rate is relatively slow, the absolute number of viable organisms which survive and persist may be large. Hence it was suggested that the maximum rate at which bacteria can be killed may have some bearing on the response of patients with subacute bacterial endocarditis to penicillin therapy.

Other investigators[2–7] have demonstrated that, *in vitro*, the bactericidal action of penicillin on various bacteria is influenced by the temperature. The purpose of the observations reported in this communication was to determine whether a slight elevation of the temperature above normal body temperature would appreciably increase the rate at which viridans streptococci are killed by concentrations of penicillin well in excess of that necessary for bacteriostasis.

PROCEDURE

Observations have been made on ten strains of viridans streptococci isolated from patients with subacute bacterial endocarditis. Two of the strains were isolated from a single patient. One of these strains (CWI) was obtained early in the course of the patient's illness; the other (CW2) was obtained about seven months later after the patient had received almost constant penicillin therapy.

One-tenth cc. of a 1:100 dilution of an overnight culture of each of the organisms to be tested was added to 1 cc. volumes of beef heart infusion broth containing various concentrations of the sodium salt of penicillin. The mixtures of broth, penicillin and bacteria were prepared in duplicate sets and incubated in water baths, one set at 37.5° and the other set at 40°C. After twenty-four hours of incubation the bacteriostatic sensitivity of each strain at each temperature was determined by observing the tube which contained the minimum concentration of penicillin and which remained clear. For control, each of the strains was incubated at 37.5°C. and 40°C. in broth without penicillin, and a hemolytic streptococcus of known sensitivity was incubated in a series of penicillin broth mixtures at the two different temperatures.

After twenty-four hours of incubation the number of bacteria per cc. in each of the tubes containing 1 unit of penicillin was determined by a serial dilution method. However, for one strain (H2) which required 8 units of penicillin per cc. for

* From the House of the Good Samaritan and the Massachusetts General Hospital, Boston, Mass.

bacteriostasis the bacterial counts were determined for the tubes containing 10 units of penicillin.

The method of preparing the broth and the penicillin solutions and the method of making the bacterial counts have been described in further detail in a previous communication.[1]

RESULTS

The results of this experiment are given in Table I. It is evident that the number of viable bacteria which persisted after exposure for twenty-four hours to an excess amount of penicillin was distinctly less in the tubes incubated at 40°C. than in the corresponding tubes incubated at 37.5°C. The relative difference varied among the different strains. Strain B was readily destroyed at even 37.5°C., and elevation of the temperature produced very little additional effect.

TABLE I
EFFECT OF TEMPERATURE ON TEN DIFFERENT STRAINS OF VIRIDANS STREPTOCOCCI

Strain	Bacteriostatic Sensitivity at		Concentration of Penicillin (units per Cc.)	Number of Viable Organisms after Incubation for 24 Hours at	
	37.5°C.	40°C.		37.5°C.	40°C.
CW1	0.03	0.04	1.0	80,000	10,000
H1	0.03	0.04	1.0	5,000	600
L	0.03	0.03	1.0	4,000	2,000
B	0.04	0.04	1.0	120	100
W	0.04	0.03	1.0	60,000	1,600
S	0.10	0.08	1.0	500	0
M	0.20	0.20	1.0	6,000	100
J	0.20	0.20	1.0	1,000	50
CW2	0.20	0.20	1.0	20,000	100
H2	8.0	7.00	10.0	8,000	5,000

In contrast to the apparent acceleration of the bactericidal activity of penicillin at 40°C. variations in the temperature, within the limits tested, did not seem to produce any significant effect upon the concentration of penicillin necessary for bacteriostasis.

TABLE II
EFFECT OF TEMPERATURE ON FOUR DIFFERENT CULTURES OF ONE STRAIN OF VIRIDANS STREPTOCOCCUS (CW2)

Culture Number	Bacteriostatic Sensitivity		Number of Viable Organisms after Exposure to 1 Unit of Penicillin per Cc. for 24 Hrs.	
	37.5°C.	40°C.	At 37.5°C.	At 40°C.
1	0.20	0.20	60,000	1,500
2	0.20	0.20	30,000	200
3	0.20	0.30	20,000	150
4	0.30	0.10	20,000	100

In Table II there are given the results of the same kind of experiment performed on four different cultures of just one of the strains of viridans streptococcus (CW2). It would appear from these data that the temperature effect on this single strain was more or less constant.

COMMENT

The *in vitro* observations reported here suggest that fever therapy in conjunction with the administration of penicillin may possibly have some application in the treatment of patients with subacute bacterial endocarditis who fail to respond to large doses and prolonged administration of penicillin alone. We have observed patients with this disease in whom it would appear that the causative organisms were inhibited and prevented from multiplying so long as large amounts of penicillin were given, but in whom as soon as the antibiotic was discontinued, even after constant administration for many weeks, the organisms again began to multiply and quickly produced positive blood cultures. In these instances it seems likely that the "persisters"[3] have the ability to lie dormant for many weeks or months and that they remain viable even

though prevented from multiplying by bacteriostatic concentrations of penicillin. If the number of persisting organisms can be reduced by the combination of fever and penicillin, there is reason to believe that some instances of penicillin failure may be converted to penicillin cures. The question of whether fever therapy in combination with penicillin will actually work *in vivo* must await clinical trial.*

The effect of an elevated temperature on the action of penicillin contrasts interestingly with the effect of sulfonamides. Previous studies[1] showed that sulfonamides may decrease the amount of penicillin necessary for bacteriostasis but do not accelerate the maximum rate at which viridans streptococci are killed. Slightly elevated temperatures on the other hand may accelerate the maximum killing rate without appreciably altering the concentration of penicillin necessary for bacteriostasis.

SUMMARY

The number of viridans streptococci which survive after twenty-four hours of exposure to penicillin in excess of the bacteriostatic concentration is much less at 40°C. than at 37.5°C.

The minimal concentration of penicillin necessary for bacteriostasis is not appreciably different at 40°C. than at 37.5°C.

The possible application of these *in vitro* observations to the therapy of subacute bacterial endocarditis is discussed.

* Craig, Schwemlein, and Kendall have reported encouraging observations on the combination of penicillin and fever therapy of early syphilis.[8]

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A Small Visual Comparator for the Determination of Plasma Volume†

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DURING the course of an investigation into the problem of shock, it became apparent that a method was needed for the determination of plasma volume which did not involve the use of expensive or elaborate equipment. The visual comparator to be described in this paper was originally developed to meet a possible war time need. It offers to any hospital or emergency ward a simple means of determining plasma volume with reasonable accuracy.

The determination of plasma volume by measuring the difference in color between serum samples taken before and ten minutes after the intravenous injection of a known amount of the blue dye, T-1824, has been described by Noble and Gregersen.[1] They have shown that the measurement of this single sample taken ten minutes after injection gives valid results both in normal subjects and in patients in shock. Since this simplified technic forms the basis of our procedure, the validity of the method in its application to other types of patients was studied in a small number of cases and confirmed. Subsequently, determinations of plasma volume were made in a large series of patients and the results obtained with the visual comparator compared with those obtained from measurements of the same sera on a Bausch and Lomb spectrophotometer.

A small visual comparator with permanent glass standards was designed for measuring the color of the ten-minute sample.* The comparator consists of a plastic housing 3.5 by 3.5 by 1.75 inches which holds two square glass tubes 10 by 10 by 95 mm. A plastic disc upon which are mounted ten colored glass standards is fitted into the square housing in such a way that the standards can be rotated in front of the tube on the left while the right tube remains unobscured. The front of the comparator is fitted with a detachable eye piece, a prism to bring the color fields into juxtaposition and a color filter to eliminate normal color differences in various sera. The back of the comparator contains a small, detachable electric lamp. (Fig. 1.)

The square glass tube containing the dye-free serum sample (obtained from the patient before the intravenous injection of dye) is placed to the left in the comparator. The dye-serum sample (obtained ten minutes after the injection of dye) is placed to the right. With the samples in place, the comparator is held close to the eye, the light turned on and the plastic disc rotated until the color field on the left matches that on the right. When the best match is obtained, the plasma volume is read directly on the outer margin of the disc where the

* The Hellige pocket comparator with prism attachment has been modified to meet the needs of this method.

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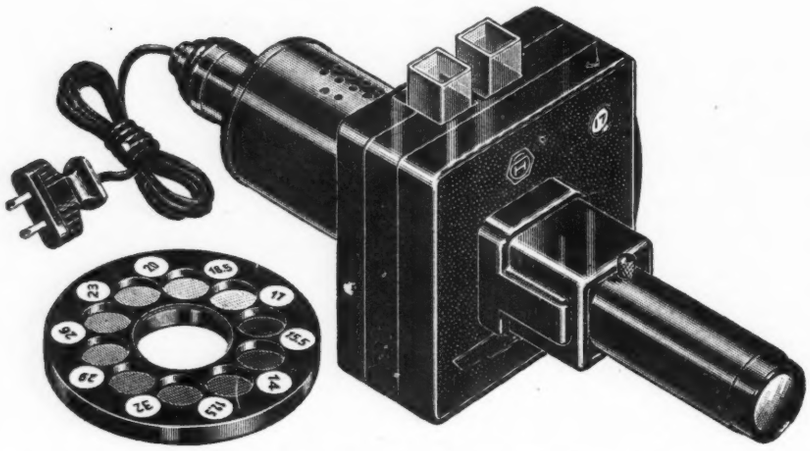

FIG. 1. *Photograph of the Hellige comparator.*

value corresponding to this color match is registered in hundreds of cc. When the dye sample does not match any of the color standards, the nearest higher and the nearest lower readings should be taken and the value obtained by interpolation.

Certain difficulties were enountered in making a set of colored glass standards which, when superimposed upon a dye-free serum sample, would match in quality and intensity the color of a serum sample containing a known concentration of T-1824. It was first necessary to make a set of liquid standards to which the permanent glass standards were to be matched. Dilutions of the dye in water or saline were not satisfactory because the quality of the color, when superimposed upon a dye-free serum sample, differed from that of a serum sample containing dye. This was due to the fact that the protein in serum changes the color properties of T-1824. Standards made up with serum were also unsatisfactory due to the presence of other colored substances in serum which vary from patient to patient. A satisfactory set of standards was finally made which employed a 4.8 per cent solution of crystalline bovine serum albumin in isotonic saline solution as the diluent for the dye. The concentration of dye in these liquid standards was determined with a Bausch and Lomb spectrophotometer using 10 mm. glass cells, and the volume corresponding to each liquid standard calculated on the basis of a 3 cc. injection of T-1824. Sixteen glass standards were made to match these liquid standards which covered a range of total plasma volumes between 1,250 and 6,800 cc. The interval between successive glass standards in the lower or "shock range" is 150 cc.; in the middle or normal range, 300 cc.; in the high or "cardiac failure" range, 400, 600 and 800 cc., respectively. The glass standards are mounted on two discs. The first disc covers a range of total plasma volumes between 1,250 and 3,200 cc. The second covers a range between 2,300 and 6,800 cc. The comparator is so designed as to permit ready interchange of discs.

EXPERIMENTAL

The validity of the results obtained by the Noble and Gregersen method for determination of plasma volume[1] was studied in six patients with various types of chronic disease. The diagnosis made in each case is listed in Table I together with the plasma volume measurements determined by the Noble and Gregersen method and by the method of Gibson and Evans.*[2]

* Four arterial samples were withdrawn at ten-minute intervals following the intravenous injection of T-1824. The dye concentration of these serum samples

It may be seen in the table that the Noble and Gregersen method gives higher values than that of Gibson and Evans. In no instance, however, does the magnitude of this difference exceed 5 per cent. These findings are in agreement with those of Noble and Gregersen and support the validity of their method in its application to various types of hospital patients.

TABLE I

PLASMA VOLUME DETERMINATIONS

COMPARISON OF VALUES OBTAINED BY TWO METHODS

Patient	Diagnosis	Gibson and Evans Method, Cc.	Noble and Gregersen Method, Cc.	Difference	
				Cc.	Per Cent
D. G.	Congenital Heart Disease	965	985	+20	2.1
G. G.	Congenital Heart Disease	1,160	1,210	+50	4.3
E. K.	Congenital Heart Disease	2,675	2,690	+15	1.8
W. H.	Laennec's Cirrhosis	4,720	4,900	+180	3.8
W. H.	Laennec's Cirrhosis	4,730	4,960	+230	4.9
W. H.	Laennec's Cirrhosis	4,590	4,740	+150	3.3
E. F.	Laennec's Cirrhosis	3,810	3,915	+105	2.8
E. F.	Laennec's Cirrhosis	3,860	3,995	+135	3.5
E. F.	Laennec's Cirrhosis	3,880	3,995	+115	3.0
J. K.	Congestive Heart Failure	3,170	3,220	+50	1.6

The reliability of the visual comparator was then tested. It was employed to measure the blue color of ten-minute samples obtained from a series of sixty-five patients. To test these results, the color of the same ten-minute samples was measured with a Bausch and Lomb spectrophotometer.

A standard procedure was followed in the study of each patient. Food was withheld for at least eight hours before each determination. (This is essential if clear serum samples are to be obtained.) In order to make sure of obtaining blood samples readily and at the exact time required, an indwelling Lindemann-type needle was inserted into the femoral artery under local novocaine anesthesia. Approximately 10 cc. of arterial blood were then withdrawn. One cc. was delivered into an hematocrit tube which contained a trace of powdered heparin. The remaining quantity of blood was divided equally between two oil coated test tubes to make sure of obtaining unhemolyzed serum samples. A No. 19 gauge needle was next inserted into a suitable vein of the forearm. If blood flowed freely from the needle, a calibrated syringe containing a known amount of T-1824 (usually 3 cc.) was attached to the needle, the dye injected and the time noted. Blood was then aspirated into the syringe and reinjected into the vein three successive times to ensure injection of all the dye. In cases of shock in which the veins were in collapse or in cases in which the withdrawal of venous blood seemed too difficult to permit adequate "washing" of the dye syringe, a three-way stopcock, attached by its side arm to a small infusion set, was interposed between the needle and the dye syringe. After injection of the dye, the handle of the stopcock was so manipulated

was determined with a Bausch and Lomb spectrophotometer using 10 mm. glass cells. The values obtained were plotted on semi-log paper against time. The best straight line was drawn through these points and plasma volumes were then calculated from the value obtained by extrapolation to the time of injection.

as to permit repeated aspiration of saline into the syringe and its subsequent injection into the vein. Exactly ten minutes after the start of the dye injection, 10 cc. of arterial blood were withdrawn from the femoral artery and again divided between two oil-coated test tubes and an hematocrit tube. In the series of six patients already referred to, three additional arterial samples were withdrawn at ten-minute intervals.

of chest operations. The remaining twenty-five subjects were medical patients on the wards of Bellevue Hospital and the Goldwater Memorial Hospital where they were being treated for chronic diseases such as rheumatic heart disease, pulmonary fibrosis and emphysema, Laennec's cirrhosis, hypertensive cardiovascular disease and bronchial asthma. The data on twenty-five consecutive determinations is given in Table II.

TABLE II

PLASMA VOLUME DETERMINATIONS

Comparison of Values Obtained with Visual Comparator and Spectrophotometer in Twenty-five Consecutive Cases

Patient	Diagnosis	Visual Comparator, Cc.	Bausch and Lomb Spectrophotometer, Cc.	Deviation from Spectrophotometric Value, Cc.
G. A.	Brain tumor—5 days postoperatively	2,650	2,680	−30
I. P.	Bronchial asthma—pulmonary fibrosis—emphysema	2,360	2,420	−60
I. P.	Bronchial asthma—pulmonary fibrosis—emphysema	2,660	2,630	+30
J. K.	Pulmonary fibrosis and emphysema	2,150	2,200	−50
M. B.	Pulmonary fibrosis and emphysema	3,000	2,900	+100
S. G.	Silicosis, second stage	3,800	3,780	+20
B. U.	Rheumatic heart disease	3,600	3,500	+100
B. U.	Rheumatic heart disease	3,800	3,740	+60
S. S.	Rheumatic heart disease	4,200	4,150	+50
L. V.	Arteriosclerotic heart disease	1,810	1,870	−60
E. D.	Coronary thrombosis	2,240	2,270	−30
T. O.	Arteriosclerotic heart disease	4,250	4,320	−70
G. G.	Congenital heart disease—age 11	1,168	1,210	−42
D. G.	Congenital heart disease—age 6	930	985	−55
E. K.	Congenital heart disease—before phlebotomy	2,850	2,790	+60
E. K.	Congenital heart disease—after phlebotomy	2,840	2,770	+70
W. H.	Laennec's cirrhosis	4,900	4,860	+40
L. V.	Mesenteric thrombosis—in shock	1,250	1,300	−50
L. V.	Same case ½ hr. after fluid replacement	1,700	1,630	+70
L. V.	Same case 3 hr. after fluid replacement	1,850	1,910	−60
S. F.	Duodenal ulcer—peritonitis	2,750	2,800	−50
S. F.	Same case ½ hr. after fluid replacement	3,200	3,150	+50
A. H.	Pulmonary tuberculosis	2,300	2,260	+40
P. C.	Pulmonary tuberculosis	2,360	2,380	−20
F. B.	Pulmonary fibrosis and emphysema	3,200	3,050	+150

One hundred plasma volume determinations were made by this method in sixty-five patients. Forty of these were patients in whom the diagnosis of pulmonary tuberculosis had been established on the Chest Service at Bellevue Hospital. Many were studied both before and after various types

In thirteen instances, values obtained with the visual comparator were higher than those obtained with the spectrophotometer, the average difference being 65 cc. In twelve instances, the comparator gave lower values, the average difference being 48 cc. For the series of twenty-five deter-

minations shown in the table, the average difference regardless of sign was 63 cc. Although the greatest discrepancies between values obtained by the two methods were 150 cc. in one case and 100 cc. in two others, in no instance did the difference exceed 5 per cent.

A similar analysis was made of the results compiled from the entire series of 100 plasma volume determinations measured with both the visual comparator and the spectrophotometer. The comparator gave higher values in forty-nine instances. The average difference was 73 cc. Lower values were obtained in fifty-one cases, the average difference being 66 cc. For all determinations, the average difference regardless of sign was 68 cc. Discrepancies between the two methods were greater than 100 but less than 150 cc. in sixteen out of 100 determinations. No single difference, however, exceeded 5 per cent.

COMMENTS

From the data derived from the small series of cases shown in Table I, it would seem probable that the results of determining plasma volumes from the ten-minute sample are as valid in patients with various types of chronic disease as they are in normal subjects or in patients in shock.

Results obtained with the visual comparator indicate that it measures the color of the ten-minute sample with a degree of accuracy sufficient to show plasma volume differences in excess of 5 per cent. The instrument, however, has certain disadvantages: First, in common with other methods it cannot be used to measure the ten-minute sample if either the dye-free or the dye-serum sample is hemolyzed. The presence of hemoglobin in either sample makes color matching very difficult. The reliability of the method depends, therefore, upon obtaining absolutely clear serum samples. Second, individual judgment plays a major rôle here as it does in all visual colorimetric methods. Some practice is necessary in order to discriminate between color differences in the high ranges.

The advantages of the comparator lie in its compact size, its low cost, and the ease and speed with which it can be used. Since it is designed to measure the difference in color between a pre- and post-injection sample, the presence of dye in the so-called dye-free sample is not an obstacle to repeated measurements in the same patient. (Tables I and II.)

In patients with congestive heart failure or in children, in whom more or less than 3 cc. of T-1824 is injected, the ten-minute sample is measured with the comparator in the usual way. However, in such instances, the true volume must be computed as follows:

$$\text{Reading} \times \frac{\text{Number of cc. of T-1824 injected}}{3} = \text{Actual Volume}$$

This calculation must be made in all instances in which the amount of T-1824 injected is not exactly 3 cc.

In practice the comparator* has been found useful as an aid in the diagnosis and treatment of shock both on the operating floor and in the emergency ward. It would seem serviceable for more or less routine clinical use in the average hospital.

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* We wish to thank Dr. S. B. Ellis of Hellige, Inc. for his invaluable assistance in constructing the glass standards and modifying the Hellige Comparator to suit our needs.

Electrocardiograms in Rheumatic Heart Disease in Children

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THE diagnosis of rheumatic heart disease in children is often difficult in early or mild cases. The clinical picture can bear a confusing similarity to that of congenital heart disease. Moreover, even when the correct diagnosis of rheumatic heart disease can be made, there remains the problem of determining whether the process is an active or an inactive one. Of the available diagnostic aids such as history, physical examination and various laboratory tests, the electrocardiographic findings are not generally considered to be sufficiently characteristic to serve as conclusive evidence.

The purpose of this paper is to draw attention to some electrocardiographic characteristics which, when present in conjunction with other clinical evidence of a rheumatic process, should be considered convincing diagnostic criteria.

Generally accepted as characteristic tracings in rheumatic heart disease are prolongation of the P-R interval, which usually means an active process though other toxic states can cause it.[1] P-R intervals greater than .16 second should be considered abnormal in children unless the heart rate is very slow.[2] Prolonged Q-T intervals likewise usually mean active disease and are less likely to be found in other conditions except those with a low blood calcium.[3] Large P_2 waves often are pointed and broad at the base, indicating auricular dilatation, and in children this is usually the result of rheumatic disease. Depression of the R-T or S-T segment and inversion of T_1 and T_2 are associated with more advanced cases. Abnormal rhythms other than sinus arrythmia, such as extra systoles, fibrillation, flutter, heart block and persistent tachycardia presuppose active and often severe rheumatic disease in children.

Some of the earliest reports of electrocardiographic findings in children with rheumatic heart disease mention the frequency of a deep S_1 wave. Krumbhaar and Jenks (1917)[4] noted large Q_2 and Q_3 waves, concluding that the $S_1Q_2Q_3$ pattern was due to the activity of the right ventricle. Their findings were based on a study of forty-two normal children, of whom thirty-three were under five years of age. The activity of the right ventricle is increased in children under five years of age, before the heart has completed its rotation to the left. What these writers did not point out is that this increased activity occurs in mitral disease in children over five years of age.

Procedure. Ninety-seven cases of rheumatic heart disease in children under fifteen years of age provided the sample for the present study. Complete charts were available in all cases, including history, physical examination, several blood counts, sedimentation rate determinations, fluoroscopic and roentgenographic reports and several electrocardiograms.

Findings. An analysis of the electrocardiographic tracings revealed the usual changes associated with rheumatic heart disease such as those enumerated above. In practically all cases, P_2 was pointed or broad at the base. Where P_2 was larger

than P_1, the percentage of cases was not calculated, although this change sometimes helps to differentiate rheumatic from congenital heart disease, in which P_1 is often larger than P_2. The QRS complex variations and the number of cases in which they appeared can be tabulated as follows:

No. of Cases	Electrocardiographic Findings
47	S_1Q_3 (some with, some without S_2 or Q_2)
11	$S_1S_2M_3$ or W_3*
4	Q_2Q_3 (mitral murmurs present)
12	Q_1S_2 (with or without Q_2 or S_2)
2	Q_1Q_2 and M_3 or W_3
2	S_2S_3 (aortic murmurs present)
6	Combined S and Q waves in two or more leads
84	S and Q waves in some form of cross combination.
13	Various other findings (described below)
97	Total

Six of the last group of thirteen cases listed above showed $S_1S_2S_3$ patterns. Some of these cases occasionally changed from an $S_1S_2S_3$ tracing to one of the cross types of wave, such as S_1Q_3 or Q_1S_3. The remaining seven cases showed large T waves, long P-R intervals, S-T displacement, T inversion or different combinations.

Beyond doubt, 86 per cent of the cases studied showed S and Q waves of the cross type of pattern. This percentage is more than three times as great as that found in a group of sixty-four cases classified as possible or potential rheumatic heart disease or congenital heart disease, in which only sixteen (25 per cent) had Q_1S_3 or S_1Q_3, and none had M_3 or W_3.

Lengthening of the P-R interval during exacerbations is found frequently but not invariably. Thirty-three of the ninety-seven cases (34 per cent) showed the P-R interval to be greater than .16 second on at least one electrocardiogram.

Large T_2 and, to a lesser extent, T_1 were found in thirty-one cases (32 per cent). Of the thirty-one cases, twenty-three (about 75 per cent) were mild or early cases.* Large T waves, when they occur alone, are found early in the process; they occur with other changes at a more advanced stage of the process. Diphasic or inverted T_1 or T_2 waves were found in only six of the ninety-seven cases, five of which were in an advanced stage.

In twenty-three cases, the S-T or R-T segment was displaced. In eight of these it was elevated; six of these were mild cases. In fifteen cases, the S-T segment was depressed; in eleven of these, the process was advanced.

The proportion of mitral to aortic lesions was about 4:1; about 10 per cent of this series of cases showed combined lesions. The S_1Q_3 or S_1M_3 or W_3 pattern was associated with the mitral lesions. Similarly associated with aortic lesions was the Q_1S_3 or Q_1M_3 or W_3 type of wave. In double lesions of the aortic and mitral valves, some variation of Q and S waves occurred in all leads. Many cases, however, show Q and S waves in the absence of any discernible valve lesions. Briefly, the Q and S waves help determine whether the strain is on the right or left heart. These findings were substantiated in a few cases by stethographic records which revealed, as expected, mitral or aortic lesions. No statistical data were gathered, however.

COMMENT

The rheumatic process involves small or medium sized vessels, while coronary occlusion generally affects vessels of large caliber. In rheumatic heart disease, anoxemia is more likely to affect a smaller area. It is not surprising, therefore, to find in this series of cases that those with depressed S-T interval, indicating anoxemia, were mostly of

* M_3 or W_3 is used to indicate a notched or diphasic QRS complex in lead 3.

* Opinion on the degree of severity of any one case was reached not on the basis of a single examination but only after progress was observed over a period of time.

the more severe type. In the presence of a complicating pleural effusion, the alteration of the S-T segment and of the T waves are superimposed upon the picture. The dilatation from toxemia may occur very early. As stated above, large T_2 waves occurred in about a third of the cases; two-thirds of these were mild or early. It cannot be overemphasized that the dilatation, from whatever cause, which accompanies an acute attack, may take one of two courses: either recovery with little damage or heart failure with permanent enlargement or death. This is what makes early diagnosis so important, not only in the frank rheumatic fever cases but in the atypical cases as well; in this connection the numerous variations rheumatic infection may take, as described in the literature, should be kept in mind.

SUMMARY

Analysis of the electrocardiographic findings in ninety-seven cases of rheumatic heart disease revealed the following: (1) 86 per cent of cases: S and Q waves of the cross type present; (2) 33 per cent of cases: lengthened P-R interval; (3) 32 per cent of cases: T_2 and, to a lesser extent, T_1 waves large; (4) 24 per cent of cases: displacement of S-T segment; (5) 6 per cent of cases: diphasic or inverted T_1 or T_2 wave present; (6) four times as many mitral as aortic lesions were found; 10 per cent of cases showed combined lesions; (7) Q and S waves were more sensitive than axis deviation in determining right or left-sided heart strain; (8) the importance of noting Q and S waves is emphasized by the fact that they occur in the cross combinations three times more frequently in children with rheumatic heart disease than in normal children or even in a group of possible or potential rheumatic heart disease cases.

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Treatment of Migraine by Intravenous Histamine*

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One of the current theories regarding the cause of migraine is that the attacks result from an allergic or anaphylactic reaction, with release of histamine into the circulation, causing in those individuals whose tolerance to histamine is low, the reactions characteristic of exposure to this substance, regardless of its method of introduction—intradermally, subcutaneously or intravenously. Furthermore it is generally believed that there are certain organs or tissues characterized by their great vascularity, especially capillaries, including skin, liver, spleen and mucous membranes (respiratory and gastrointestinal tracts) which may be designated as shock organs, and even though remote from the source of histamine formation, may respond in a characteristic manner to minute quantities by vasodilatation, with clinical phenomena such as urticaria or asthma. Endothelium and, through the carotid arteries, the brain, can be classified as shock organs, and it is in this category that migraine may be placed. These organ responses may be evoked by production and release of histamine from many causes—trauma, changes in temperature, chemicals or bacterial toxins, or by an allergic reaction otherwise not particularly noted.

In the circulating blood, histamine remains but momentarily, being rapidly taken up by the cells, where in sufficient concentration it causes its characteristic responses. Quantitative determination is thus extremely difficult, and little data are at hand regarding the concentration necessary to produce reactions in sensitive and non-sensitive subjects.

The fallacy of the intradermal histamine test lies in the peculiar and poorly understood pharmocological action of that substance. While it causes vasodilatation of the face, neck and shoulders, there is a corresponding constriction in the hands, legs and splanchnic areas, to the extent that there may be a lowering of skin temperature of 5°C. in the feet, with corresponding conservation of body heat and systemic blood pressure offsetting the loss from the flushing areas. With this sensitive gradient from shoulder to wrist, a slight alteration in the location of the intradermal injection will result in definite and significant variations in the size and character of the reaction. Furthermore, the degree of reaction depends on both body and external temperatures, such that, with identical injections in each forearm, a blanket placed over one such area will cause the reaction to become two to five times the intensity of the uninsulated area on the other arm. Disregarding all such variable factors, this reaction is minimal in brunettes, great in blondes and maximal in red heads.

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It has been the contention of many, including the authors, that there are two types of migraine, the vasodilated and the vasoconstricted. This is borne out by well recognized features of both etiology and by treatment of individual attacks. In a relatively high percentage of cases parenteral ergotamine tartrate administered early in the cycle will ameliorate or terminate the attack, whereas there remain a substantial number who either obtain no relief or experience aggravation of their symptoms from this medication, regardless of having received it early or even on anticipating an attack. Obviously, the former are in a state of vasodilatation and respond to a vasoconstrictor. Furthermore many of these patients, unresponsive to ergotamine, experience prompt and sometimes lasting relief from vasodilators, particularly nitroglycerine, nitrites and nicotinic acid. Experience with alcohol indicates that many persons are certain to precipitate an attack of migraine with as little as one cocktail (vasodilators), while others obtain definite relief from one or two drinks.

Atkinson,[1] after testing twenty-one cases of migraine by the standard intradermal histamine test, found contrary to his experience in Ménière's disease, that there were no hyper-reactors, or as generally interpreted, vasodilators, and that every one exhibited a primary vasoconstrictor mechanism. He believes that there is a primary constriction followed by vasodilatation causing the headache and advocates an early attack by nicotinic acid, rather than waiting for the secondary vasodilatation and then treating that phase with a potentially dangerous vasoconstrictor. This is at variance with the generally confirmed fact that use of ergotamine tartrate, a vasoconstrictor, very early (with the first intimation of aura, or in anticipation of attacks expected because of cycle, dissipation, indulgence in food known to be harmful, or impending menstrual cycle) will ameliorate or defer an attack, whereas delay in its use results in diminished or total loss of effect.

Wolff[3] has demonstrated that after a period of pulsation, the branches of the external carotid become rigidly dilated, after which vasoconstrictors are of little or no value, and that pain derives from sustained contraction of muscles of the scalp and neck, which contract reflexly from the pain of vascular origin.

It seems fitting to make a few observations at this point before proceeding to the next phase of the study of migraine: (1) Histamine cephalgia, as described by Horton, is due to dilatation of branches of the internal carotid artery, and the attacks may be relieved by spinal puncture and raising the intrathecal pressure to 700 mm. of water. (2) Pre-headache, aura, prodromes, scotomata, are due to vasoconstriction of branches of the internal carotid, are cortical in origin and involve chiefly cranial, especially sensory nerves. (3) Migraine headache involves principally and eventually vasodilatation of the branches of the external carotid artery, particularly the superficial temporal and occipital, less frequently middle meningeal and internal maxillary.

To study this aspect of the mechanism further, we have instituted careful study of the retinal vessels in order to ascertain if any reflection of the state of the cerebral vessels (carotid and branches) can be determined. With the cooperation of members of the Department of Ophthalmology, we have studied eye grounds during intervals between the attacks, and when possible persuade patients to present themselves to us, in the hospital or offices, at the first premonition of an attack. Careful observations with accurate notes upon the state of retinal vessels are carried out at frequent intervals, in some instances without therapy, in others with our various therapeutic agents. Frequently with administration of intravenous

histamine, typical headache of great severity will result, necessitating decreasing the rate of flow or its discontinuance, during which times frequent examinations of eye grounds can be carried out, observing the state of the vessels during prodromal stages, at the height of attack, and when relieved by nicotinic acid or ascorbic acid.

Results showed no single case in which there was vasodilatation of the retinal vessels even when there was flushing of the skin due to intravenous histamine injection. A large proportion of the cases showed no observable change in the diameter or state of the vessels. However, a few cases showed very definite, and in some cases, marked vasoconstriction of the arteries and arterioles of the retina, the vasoconstriction being intermittent in character and involving all areas of the retina visible to us. These patients were not hypertensive and examinations between attacks of migraine without therapy showed normal eye grounds with no such contractions.

It seems that the contention that histamine vasodilatation involves chiefly the branches of the external carotid artery is correct. However, vasoconstriction observed in these few cases did indicate that at times the widespread vasoconstriction postulated in migraine may involve the ophthalmic branch of the internal carotid.

Much confusion of thought exists regarding the mechanism of histamine therapy, especially with reference to the term "desensitization," which in this context is ambiguous and leads to erroneous concepts. Consequently, we believe the term "desensitization" should be restricted to conditions of true allergy, or the anaphylactic status, in which antibodies exist as the result of previous exposure or reaction to an antigen by whatever route, with the response to subsequent exposures characteristic of the shock organ or organs involved (asthma, hay fever, urticaria, etc.).

While not allergists, we believe, as do immunologists, that an antigen must first, be protein in character, and secondly, consist of an aggregate above a somewhat loosely demarcated zone in the scale of protein degradation. Thus, albumin, globulin, and albumoses with relatively enormous molecules, are antigenic with great immunological specificity, while ascending from the low end of the scale, amino acids and peptone are non-specific and non-antigenic. They may be injected or absorbed through various channels without production of antibodies and without resulting anaphylactic reactions. Somewhere in the polypeptid range, this specific antigenic property makes its debut, and becomes increasingly potent and specific as each protein molecule assumes its characteristic configuration.

With these facts in mind, we can neither assume that histamine, which is decarboxylated histidine (an amino acid) could produce a state of sensitization or allergy, nor that its parenteral administration can desensitize in the accepted meaning of the word.

Therefore, we must conclude that these individuals are not sensitized but exhibit degrees of lowered tolerance to histamine, and that successful therapy results from the production of an increased tolerance, either physiological as in the case of alcohol, tobacco, caffein and numerous drugs, or quite probably from the increased production of histaminase, which does not prevent the formation and release of histamine, but is mobilized and available to neutralize or destroy that substance. Keeping further in mind the rapidity with which histamine disappears from the blood, it becomes clear why its long continued administration intravenously, to the limit of the patient's capacity, often for a period of six to ten hours, will be more effective in creating an increased tolerance than repeated injections

which result only in a very brief exposure to its action.

Rainey's[2] report of a number of cases of Ménière's disease unsuccessfully treated with subcutaneous injections of histamine, which were benefited by its prolonged intravenous administration, encouraged us in our point of view. Histamine remains for only a brief time in the blood, being rapidly taken up by the cells in which it is normally found. Hence, it is to be presumed that brief exposure, such as result from single injections, cannot effect any great increase in tolerance to histamine.

Presuming that the source of histamine is an allergic or an anaphylactic reaction, is it necessary that this reaction be specific to one or more definite proteins? Suppose that we say that it is not, and that certain individuals lack the capacity to decompose some, many or all proteins to the amino acid level, or at least below the antigenic aggregate. This point of view is reflected by the fairly general failure of skin tests for food allergies to solve the problem of migraine. Occasional brilliant results from such tests, or elimination diets, are well recognized, but the great majority of cases give no clue to specific foods. Why is it not probable that these individuals with no definite results from such tests, have an inability completely to break down protein aggregates to their simple components, and periodically build up a state of anaphylaxis which is released by an attack of migraine, much as desensitization is accomplished?

SELECTION OF CASES

We have used no patients in this series who could conceivably have headaches from any other cause, such as sinusitis, neuralgia of the face or scalp, hypertension, infection, skull injury, eye disease or brain tumor. To date we have accepted patients only with headaches of great severity or those of moderate to great severity. All doubtful cases have been rejected in this series.

Migraine headaches are paroxysmal, usually unilateral, temporal and post-orbital. Characteristic of the condition is freedom from any symptoms between attacks. Headaches are usually, but not invariably, preceded by aura or prodromes, appearing from six hours or more to within a few minutes of the onset, involving particularly sensory cranial nerves, predominantly vision, hearing or equilibrium, taste and smell, with various cutaneous sensations. At times objective changes, such as dryness of the skin or a distinctive body odor perceptible to others may be noted. Familial history is frequent, and numerous observers report that inheritance of migraine from the paternal side is usually more severe than from the distaff line. Evidence of allergy to specific foods, notably chocolate, and of other allergic states such as hay fever and urticaria is common. Freedom from attacks in pregnancy after the first trimester is almost universal. Attacks usually involve nausea and vomiting or nausea alone.

Migraine equivalents are frequently encountered either as a complete change in pattern of the attack, or as totally unrelated to sick headaches. Dr. Post, and one of the authors (W. A. T.) in 1924 indicated that paroxysmal tachycardia was in practically all cases a migraine equivalent, or cardiac migraine, and collected nearly fifty cases in which the tachycardia entirely replaced the typical headache, or for longer or shorter periods alternated with the headache. Vasovagal attacks (Gower's "Borderland of Epilepsy") are largely constituted of prodromes or aura which fail to materialize as a full blown attack.

Determination of specific food allergies by elimination diets is made difficult by a refractory period. Patients, after partaking of food known definitely to produce an attack, may thereafter for a period of from

two to eight or ten days indulge further without ill effect.

Treatment. All patients are now treated by the intravenous injection of 1 mg. of histamine base as histamine acid phosphate diluted in 500 cc. of physiological salt solution. The initial method of giving three such treatments on alternate days has now been gradually modified to giving six injections on successive days. Injections are given very slowly, about five drops per minute, at the beginning and the rate increased or modified according to the individual response. The entire procedure takes from three to eight or more hours. When possible the rate is increased to thirty or even forty drops per minute, in which case three to four hours will suffice. Blood pressure is taken every half hour, and any decided drop is considered an indication for reduction of the rate or termination of that treatment, usually temporarily. Too rapid an injection will result first in flushing of the face, later the chest and shoulders, often tachycardia, and finally a typical headache, mild to severe, which may be relieved by slowing the rate, or by injection directly into the tubing or otherwise of epinephrine or ascorbic acid (1,000 mg.). The onset of urticaria or asthma is an indication for similar procedures.

Gastric analysis, done in most of the recent cases, shows a very high acidity with a large amount of secretion, as compared with fasting or control aspirations. With half-hour aspirations or continuous aspirations, the patients experience no distress, otherwise many complain of heartburn, which is relieved by alkaline powder, or prevented by routine frequent feedings and powder. Two hemorrhages from unsuspected ulcers have constrained us to careful histories and adequate acid control. Precautions must necessarily be taken in the long continued use of a substance having such marked effects on circulation and gastric acid secretion, particularly the danger of thrombosis in event of falling blood pressure and decreased velocity of blood flow. No patients were treated in which hypertension, or cardiac or renal impairment were found to exist, or in which there was evidence of mental or central nervous system disease. Evidence of increasing tolerance was almost universally present in the rate of flow at which successive doses were tolerated. Many patients were unable to take more than 50 to 100 cc., usually because of severe headache, at the rate of five drops per minute at the first treatment, and tolerated progressively larger amounts at a more rapid rate until the entire 500 cc. was taken. Only then was the course of treatment considered started and four or more additional doses given.

EVALUATION OF RESULTS

Evaluation of results has not been arrived at haphazardly, with each of us having possibly different standards or ideals, but from analysis of objective statements by the patients from a follow-up questionnaire sent every three months.

This questionnaire contains data as to dates of treatment, filled in by us with the patient's name and hospital number. They report:

My headaches are:

Well—better—unchanged—worse—with other columns for:

Frequency
Severity
Duration
Nausea and vomiting
Prodromes

Data as to relation of relief to treatment:

Hospital treatment
Later treatment

Space below for expression of own opinion regarding success or failure of treatment—of actual attacks, modifications of attacks, aura, etc.

Classification of Results. We have found four different types of response as far as relief is concerned: (1) Those whose relief was immediate—complete and apparently permanent (up to three years eight months); (2) those whose relief was immediate and complete, but whose headaches recurred after weeks or months, and which were subsequently improved or relieved by subcutaneous injections of histamine or by repeating the intravenous program; (3) those who did not experience immediate relief after the intravenous treatments, but who gradually obtained complete or satisfactory relief either spontaneously or by later subcutaneous injections of histamine; and (4) those who obtained no relief.

TABLE I
CRITERIA FOR SELECTION OF CASES OF MIGRAINE

They are:
- Paroxysmal
- Usually unilateral—post-orbital, supra-orbital or occasionally occipital

The patient is:
- Free of symptoms between attacks
- Free of symptoms during second and third trimesters of pregnancy
- Frequently allergic

The aura:
- May involve all sensory cranial nerves, especially II (scotomata, blindness, diplopia, hemianopsia) VIII (deafness, tinnitus, vertigo, equilibrium) I (smell)
- Cutaneous sensory, pruritis, subjective changes in temperature

Equivalents:
- Paroxysmal tachycardia
- Vasovagal attacks

One hundred four patients with pure migraine of great or moderate severity have been treated. The definite values for age, sex, age of onset and duration are essentially similar to the statistics of seventy-five cases reported in the Bulletin of the New York Academy of Medicine, March, 1946. No patients have been treated whose attacks were not sufficiently severe to interfere with routine daily life, expectancy of meeting engagements or obligations.

TABLE II

No. of patients	104
Sex—Male	17
Female	87
Average age	36 years
Average age at onset	19 years
Average duration of migraine	20 years
Average length of attacks (excluding cases of migraine state)	25 hours

TABLE III
RELIEF OBTAINED

Relief	Mod. Severe	Very Severe	Total
Complete, permanent	14	28	42
Complete, temporary	6	10	16
Partial	18	16	34
None	7	5	12
Total	45	59	104

CONCLUSIONS

A method found successful in histaminic cephalgia and in Ménière's disease has been applied to approximately 100 cases of severe headache due to migraine. The results have been satisfactory and an improvement may be found in longer continued injection, perhaps twenty-four hours at each treatment.

In a process which is potentially dangerous, both from increased gastric acid production and possible collapse from decreased blood pressure, it is important to choose for treatment only those cases that cannot be other than migraine and are of moderate to great severity.

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Case Reports

Hypothyroidism and Mild Myxedema from Thiocyanate Intoxication

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SIGNIFICANT thiocyanate toxemia rarely occurs if the dose of thiocyanate is carefully regulated. However, in a few cases in which thiocyanate was being taken, hypothyroidism and myxedema have developed. In the case we are reporting, careful observations were made both before the onset of toxemia due to potassium thiocyanate and after recovery from it.

CASE REPORT

The patient, a white woman, sixty-two years of age, was admitted to the Mayo Clinic, June 19, 1945, with the complaint that her eyelids had become puffy in recent months. She had been seen at the clinic on six previous occasions since January, 1941, mainly for treatment of uncomplicated essential hypertension.

The patient had started taking potassium thiocyanate, 6 gr. (0.4 Gm.) per day in December, 1941. Two subsequent examinations between that date and June, 1944, had revealed a satisfactory clinical course. Clinical and laboratory findings for the entire study are recorded in Table 1. The concentration of cyanate in the blood plasma during this period varied between 3 and 4 mg. per 100 cc. However, inasmuch as the patient's blood pressure varied between 145 mm. of mercury systolic and 85 mm. diastolic and 180 mm. systolic and 100 mm. diastolic with this concentration of cyanates, increased dosage was not advised at these visits.

In June, 1944, the patient returned to the clinic for examination. Her blood pressure was found to be 190/104. The level of cyanate in the blood plasma was 3.1 mg. per 100 cc. Physical examination gave essentially negative results and the findings were not changed significantly from those recorded on previous admissions. Routine tests on blood and urine gave results within normal limits. The level of the blood urea was reported as 24 mg. per 100 cc. Roentgenographic examination of the thorax on June 5, 1944, revealed slight cardiac enlargement (Fig. 1) due to the slight increase in size of the left ventricle. An electrocardiogram taken on the same day (Fig. 2) gave evidence of left axis deviation and upright T waves in all three standard leads. No significant change from those taken previously was found. The patient was dismissed after being instructed to increase the dose of potassium thiocyanate to 9 gr. (0.6 Gm.) per day.

The onset of puffiness of the eyelids occurred in October, 1944. The puffiness was constant and gradually increased after onset. The patient's friends had recently remarked about a change in her facial features and she had noticed an occasional lisp or thickness of the tongue when she talked. She also complained of easy fatigue and persistent drowsiness. She denied that she had intolerance to cold, dryness of the skin, dry falling hair or any symptoms or signs of cardiac decompensation. Examination by systems failed to reveal any additional pertinent information.

Physical examination on June 19, 1945, revealed an active woman with a facies suggestive of that associated with myxedema—puffy eyelids, thickened lips and a rather dull facial

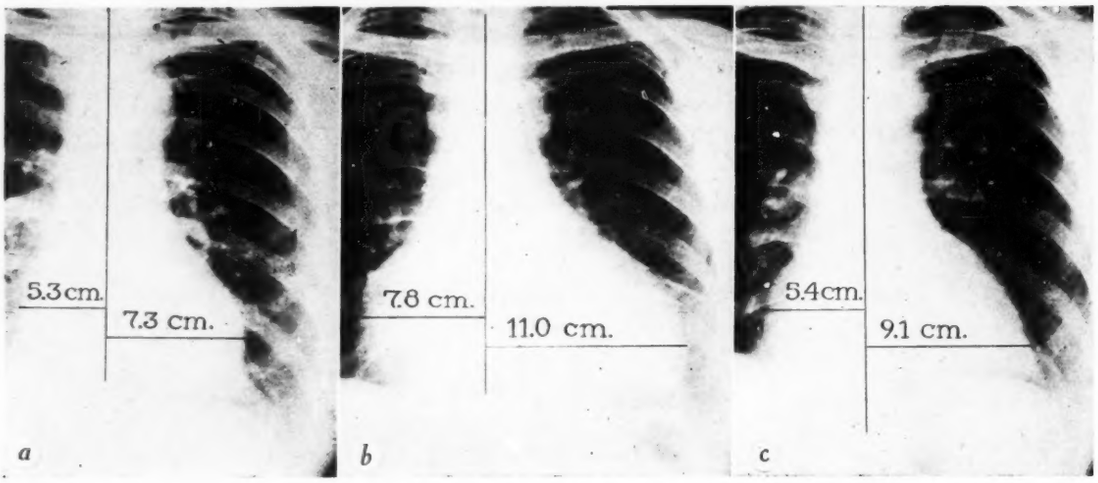

FIG. 1. *Roentgenograms of thorax delineating heart shadows before and after cyanate intoxication. a, June* 5, 1944, *one year before intoxication. Slightly enlarged heart commonly seen in patients who have essential hypertension. b, June* 20, 1945, *in the course of intoxication. Relatively a much larger heart shadow than in a. c, August* 16, 1945, *after recovery from intoxication. Relatively a much smaller heart shadow than in b and approximating that in a.*

expression. (Fig. 3*a* and *b*.) Dryness and increased elasticity of the skin were noted. The thyroid gland, although firm and slightly nodular, was not distinctly abnormal in size or shape. The heart was enlarged to both left and right. (Fig. 1*b*.) The apex beat was diffuse and was located 13 cm. to the left of the midline in the fifth costal interspace. On percussion the right border of the heart was estimated to be 3.5 cm. to the right of the midline in the fourth costal interspace. The heart tones were of relatively poor quality. The first apical tone was muffled and split; the second pulmonic tone was moderately accentuated, and the second aortic tone was slightly accentuated. No cardiac murmurs were heard and the cardiac rhythm was regular. Blood pressure was recorded as 175/110 and the pulse rate was 88 beats per minute. Examination of the lungs, abdomen, pelvis and rectum failed to reveal any significant abnormality. A hard, painless, immovable mass was found in the right thigh. There was no dependent edema. The deep reflexes were normal and the slow release phase which is seen frequently in patients with myxedema was not present.

Laboratory examination revealed essentially normal findings for blood and urine (Table 1) except for the level of cholesterol which was 277 mg. per 100 cc. of plasma. The concentration of cyanate in the blood plasma was reported to be 4.9 mg. per 100 cc. This concentration was lower than that considered optimum for therapeutic effects.* The basal metabolic rate was −10 per cent on June 21, 1945, and −9 per cent on June 25. On June 20, roentgenographic examination of the thorax revealed definite enlargement of both the right and left ventricles. The cardiohepatic angle was acute. Roentgenologic examination showed that the mass in the right thigh was a bowing of the upper part of the femur due to Paget's disease involving the right femur and the right innominate bone.

Electrocardiographic findings on June 23, 1945, (Fig. 2) consisted of: a cardiac rate of 64 beats per minute, sinus bradycardia, slurred QRS complexes in leads I, II and III with abnormally low total voltage, left axis deviation and shallow, inverted T waves in lead I, isoelectric T waves in lead II and III and diphasic T waves in precordial lead CR_5.

A tentative diagnosis of hypothyroidism with mild myxedema due to administration of potassium thiocyanate was made. Administration of this drug was stopped and the patient was instructed to drink 2,400 cc. of water per day in an effort to eliminate the cyanates from the body fluids. No iodine or thyroid extract was administered.

* We usually advise a plasma concentration from 8.0 to 12.0 mg. in 100 cc.

The patient was seen several times by the clinician in a period of eight weeks and serial electrocardiograms, roentgenograms of the thorax, determinations of basal metabolic rate and concentration of cyanate in the blood plasma were made. (Table 1.) Within this period the puffiness of the eyelids, malaise, fatigue and the defect in speech disappeared. The patient's features and expression returned to normal. (Fig. 3*c* and *d*.) The basal metabolic rate rose gradually to a level of +9 per cent. The heart decreased to approximately the size it was in June, 1944. (Fig. 1*a* and *c*.) The electrocardiograms revealed an increase in the total voltage of the QRS complex to a normal level and, more important, they showed a reversion to positive T waves of normal amplitude in all leads. The level of potassium thiocyanate in the blood plasma fell to less than 1 mg. per 100 cc. fifteen days after the administration of the drug was stopped. The level of the blood cholesterol fell from 277 to 234 over a period of eight weeks. (Table 1.)

The final diagnosis was hypothyroidism with mild myxedema due to administration of potassium thiocyanate for essential hypertension.

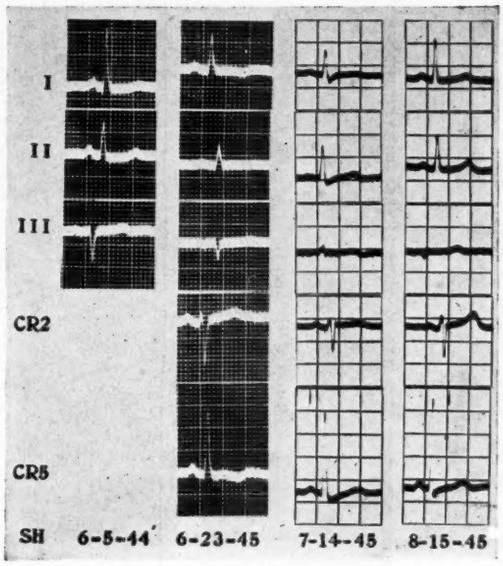

FIG. 2. *Electrocardiographic tracings. June* 5, 1944, *one year before cyanate intoxication. The standard leads reveal left axis deviation. June* 23, 1945, *during cyanate intoxication. Left axis deviation, decreased voltage, inverted* T *waves may be noted in lead* I, *isoelectric* T *waves in leads* II *and* III. *In chest lead* CR_5, T *waves are diphasic. July* 14, 1945, *during recovery from cyanate intoxication. In leads* I *and* III, T *waves are diphasic. In lead* II *they are slightly upright. In chest lead* CR_5, T *waves are upright. August* 15, 1945, *after recovery from cyanate intoxication. In the standard leads voltage is increased and voltage and* T *waves are similar to those on June* 5, 1944. *Also* T *waves are upright in chest leads* CR_2 *and* CR_5.

REVIEW OF THE LITERATURE

Since the introduction by Pauli in 1903 of sodium and potassium thiocyanate for the treatment of essential hypertension, these drugs have had widespread, if at times sporadic, use. Numerous articles have been written concerning both their efficacy and toxicity; and although diverse features of the latter have been reported since 1925, first mention of a toxic effect on the thyroid gland of man was made by Barker[3] in 1936. At that time he reported three cases of "peculiar myxedematous swelling of the tissues of the face, orbital areas and cervical regions." Two of these three patients had enlarged thyroid glands. The basal metabolic rates of the three patients ranged from −9 to −18 per cent. In 1941, Barker and his associates[4] reported a series of 246 cases in which the patients had received thiocyanate for periods varying from two to ten years. Enlargement of the thyroid glands developed in eleven of these cases and myxedematous facies in nine. The basal metabolic rates of these patients were moderately reduced to approximately —10 per cent. All of these patients recovered within two weeks when 1 to 2 gr. (0.065 to 0.13 Gm.) of thyroid extract was given per day.

In 1942, Fahlund[6] observed painful enlargement of the thyroid gland as an acute manifestation of thiocyanate toxemia. After eight days of treatment with thiocyanate, enlargement of the gland occurred and was accompanied by urticarial dermatitis, nausea, vomiting and diarrhea. The entire process subsided in one week after the administration of thiocyanate was stopped. Kobacker,[11] in 1942, noted a case of goiter

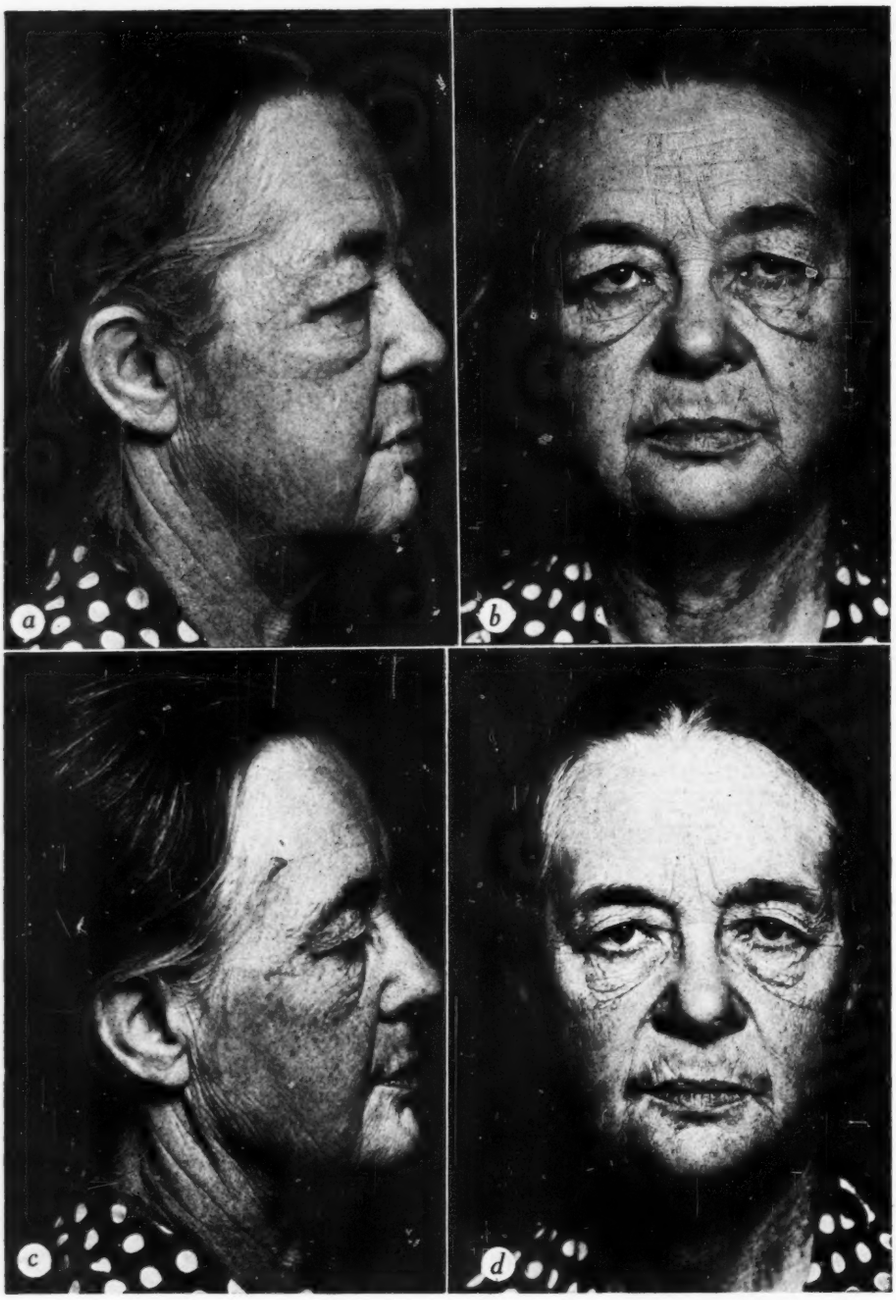

FIG. 3. *a and b, photographs made June* 23, 1945, *when thiocyanate intoxication was present; c and d, side and front views after recovery from intoxication; photographs were taken on August* 15, 1945.

and myxedema associated with thiocyanate therapy. When treatment with thiocyanate was stopped and thyroid extract was given, the thyroid gland decreased in size and signs of hypothyroidism with myxedema disappeared. The goiter and myxedema recurred when thiocyanate was administered again.

Foulger and Rose,[8] in 1943, reported a case of acute goiter which occurred from administration of thiocyanate.

Rawson, Hertz and Means,[17] in 1943, reported two cases of goiter caused by thiocyanate. They observed that these goiters were accompanied by clinical symptoms of

hypothyroidism and levels of plasma protein iodine in the range compatible with myxedema. Exophthalmos and lid lag developed in one patient. These investigators were fortunate in obtaining a specimen of the thyroid gland of one patient for biopsy. This revealed an extremely hyperplastic thyroid gland with marked papillary overgrowth. After cessation of the administration of thiocyanate, clinical and laboratory signs of hypothyroidism disappeared and the goiter receded in one case. All of these signs recurred when thiocyanate was administered again. In both cases, the administration of thyroid extract was followed by disappearance of the goiter and hypothyroidism, although administration of thiocyanate was continued.

In the discussion of their paper Rawson, Hertz and Means cited experimental evidence that thiocyanate goiters cannot be produced in laboratory animals if iodine is

TABLE 1

CLINICAL AND LABORATORY FINDINGS*

Date	Blood						B.M.R., Per Cent	Roentgenogram of Thorax†	E.C.G.†	Edema of Eyelids, Grade‡
	Whole Blood			Plasma		Serum				
	Leukocytes, per Cubic Mm.	Hgb., Gm. in 100 Cc.	Urea, Mg. in 100 Cc.	Cholesterol, Mg. in 100 Cc.	Cyanate, Mg. in 100 Cc.	Sulfate, Mg. in 100 Cc.				
1941										
Feb. 13§‖	8,300	13.1								
Dec. 5	....	....	26							
Dec. 11	....	....	..	...	3.5					
1942										
Apr. 22	....	....	..	...	3.4					
Nov. 28	7,000	12.3	38	...	3.4					
1944										
June 5	9,500	13.3	24	...	3.1	...	..	+	+	
1945										
June 20	....	11.6	26	277	4.9	...	..	+		
June 21	5,600	....	..	...	...	...	−10			
June 23	....	....	..	...	...	...	..	..	+	2
June 25	....	....	..	...	...	...	−9			
July 5	....	....	..	...	...	...	..	+		
July 7	....	....	..	...	Less than 1.0	...	..	..	..	1
July 9	....	....	..	...	...	...	0			
July 14	....	....	..	...	...	...	..	+	+	1
July 16	....	....	..	...	...	...	+1			
Aug. 15	....	....	..	...	...	...	..	..	+	0
Aug. 16	....	11.7	..	234	Less than 1.0	6.1	+9	+		
Aug. 17	....	....	32							

* Negative results of routine urinalyses reported on Feb. 14, Dec. 5 and 11, 1941; Apr. 22 and Nov. 28, 1942; June 6, 1944; June 20 and Aug. 17, 1945.

† Plus indicates that roentgenograms of thorax or electrocardiographic tracings were taken.

‡ Grading basis of 1 to 4 in which 1 represents the least and 4 the most edema.

§ 4,670,000 erythrocytes per cubic mm. of blood.

‖ Feb. 14, 1941, flocculation test in serum for syphilis negative.

administered concurrently. They concluded that thiocyanate goiter in man can probably be prevented by the administration of iodine in prophylactic doses. They stated definitely that the symptoms of thiocyanate goiter can be relieved by administration of thyroid extract even when the administration of thiocyanate is continued.

Potter[16] recently reported two cases of acute goiter occurring in the course of administration of thiocyanate. He was privileged to examine tissue from both of the thyroid glands grossly and microscopically. These thyroid glands were hyperplastic. The acini were uniformly small and contained little or no colloid. The acinar epithelium was high cuboid or columnar, but no papillary infolding, vacuolization of colloid nor lymphoid follicles which are so commonly seen in toxic diffuse goiter were present.

Since Zondek,[21] in 1918, first described the occurrence of an enlarged heart associated with the syndrome of hypothyroidism with myxedema, a rather voluminous literature on the subject has accumulated. A compilation of facts presented by many authors leads to certain conclusions regarding the character of cardiac involvement in myxedema. The enlargement of the heart involves all four chambers. The myocardium, as determined by roentgenoscopy, contracts sluggishly and bradycardia is a frequent feature. Whether congestive failure is ever the result of myxedema alone is a controversial point. Zondek, Assmann[1] and Fahr[7] have reported such cases of congestive failure. Fahr stated that in 75 per cent of seventeen cases of myxedema which he reported there was evidence of heart failure. On the other hand, Christian[5] and Ayman, Rosenblum and Falcon-Lesses[2] were unable to attribute congestive failure to the myxedema heart. Willius and Haines[20] in a series of 162 cases of myxedema could not find justification for the establishment of a cardiac syndrome characteristic of myxedema. However, at the time of this study teleoroentgenograms of the thorax were not made.

Many electrocardiographic abnormalities have been associated with the heart in myxedema. Absence or low amplitude of P waves, prolonged P-R intervals, QRS complexes of low total voltage, and T waves of low amplitude or inverted T waves have all been reported by several authors. However, according to White,[18] the most significant and almost pathognomonic electrocardiographic abnormality of the so-called myxedema heart is the change in the T waves in all leads. They may become low in amplitude, iso-electric or inverted.

The cause of the electrocardiographic changes seems to be dependent on a change in the conductivity in the heart itself. Lueg[13] and Nobel, Rosenblüth and Samet[15] considered that the electrocardiographic changes may have been due, in part at least, to changes in conductivity of the skin when myxedema is present. Moschcowitz[14] noted low QRS potentials and T waves of low amplitude in cases of edematous scleroderma, nephrosis with edema, myxedema and ichthyosis. Hallock,[9] however, in studying the electrocardiograms of persons with scleroderma and ichthyosis, failed to note these changes. White[19] by the use of needle electrodes, found that the electrocardiographic changes of the so-called myxedema heart were not due to changes in the skin.

A difference of opinion exists concerning the pathologic changes in the heart in myxedema. Cardiac enlargement in myxedema has been attributed to hypertrophy, dilatation or pericardial effusion. At present the consensus is that the essential change is dilatation. This dilatation has been ascribed to such various causes as watery imbibition of the myocardium, decreased sensitivity of the myocardium to nervous impulses or absence of a specific circulatory stimulant. LaDue,[12] in 1943, described the microscopic changes.

He noted hydropic vacuolization, loss of striation, branching, pyknotic nuclei and irregularity in staining properties of the muscle fibrils. However, he stated that these changes were not specific.

COMMENT

This report adds another case to the growing list of cases in which the administration of potassium thiocyanate has an effect on the thyroid gland in man. Several features are worthy of note. One year previous to the onset of mild myxedema with cardiac manifestations this patient had been examined at the clinic. At that time electrocardiograms, roentgenograms and other records were made which have been valuable as controls. As far as we have been able to discover, this is the only case of myxedema with classical cardiac complications in which control observations have been available. Howell,[10] in July, 1945, reported that one patient had been observed previous to the onset of myxedema, but the cardiac enlargement attributable to myxedema was slight and the characteristic electrocardiographic findings were not present.

The generalized increase in the size of the heart with an acute cardiohepatic angle, is characteristic of the myxedema heart. The electrocardiogram revealed the typical abnormality of T waves, which, according to White,[18] is almost pathognomonic of myxedema. It is interesting to note that the heart decreased in size to its previous dimensions within a period of eight weeks even under the constant strain of an existing hypertension. This is a splendid example of the recuperative power of the myocardium and evidence against a possible assumption that the temporary cardiac enlargement was due partially to pre-existing ventricular strain.

In this case many of the features of hypothyroidism caused by thiocyanate noted by other authors were present. The basal metabolic rate was only moderately reduced, the level of plasma cholesterol was slightly elevated and of blood cyanate was consistently low. The myxedema was mild except for the cardiac changes. The facies was definitely myxedematous and the skin was dry. However, the patient did not complain of intolerance to cold, her mental capabilities were not affected and the slow release phase of deep reflexes could not be demonstrated. In contrast to most other reports, no thyroid enlargement was apparent. Recession of the hypothyroidism with myxedema occurred merely on withdrawal of thiocyanate, without administration of iodine or thyroid extract and the thyroid gland resumed its normal function.

It is interesting to correlate the level of cyanates in the blood with the electrocardiographic and roentgenologic data in this case following cessation of administration of potassium thiocyanate. By July 7, 1945, the concentration of cyanate in the blood plasma had decreased from 4.9 mg. in 100 cc. to less than 1 mg. On July 9, 1945, the basal metabolic rate increased from −9 per cent to 0. However, on July 14, 1945, the transverse diameter of the heart as shown in the roentgenogram was 18.5 cm., which was approximately what it had been on June 20, 1945, and there also had been only minor changes in the electrocardiographic tracings. During the interim of one month, from July 14, 1945, to August 16, 1945, the basal metabolic rate increased further to +9 per cent; the transverse diameter of the heart in the roentgenogram decreased to 14.5 cm. and the T waves in the electrocardiographic tracings became upright. Thus, after cessation of administration of thiocyanate and the almost complete disappearance of this substance from the blood plasma, there was a latent period during which the only significant change was a slow rise in the basal metabolic rate. These results seem to be good evidence that the various abnormal factors noted in this

case were due to the effect of thiocyanate on the thyroid gland.

In addition to the effect on the thyroid gland, two other features of thiocyanate intoxication were present in this case. The concentration of hemoglobin in the blood was decreased and it did not increase in eight weeks after administration of thiocyanate was stopped. The level of sulfate in the serum on August 16, 1945, was 6.1 mg. per 100 cc. Elevation of serum sulfate to about this level, occurring coincidentally with administration of thiocyanate, has been noted in three cases at the Mayo Clinic.

SUMMARY

The patient whose case is reported herein developed hypothyroidism with mild myxedema in the course of prolonged administration of thiocyanate for essential hypertension. Classical cardiac manifestations of myxedema occurred and could be compared with control records made one year previously. Spontaneous, subjective and objective improvement occurred after cessation of thiocyanate therapy. The temporarily enlarged heart receded to dimensions approximating those previously present.

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Congenital Hemolytic Jaundice in a Negro Family*

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A NUMBER of authors[1–5] have stated that congenital hemolytic jaundice occurs in any race but an examination of the literature indicates that the disease is very uncommon in the negro, and perhaps also in the oriental.[6] Wintrobe[7] notes the extreme rarity of the condition in the negro, and in his large experience encountered but one example, in a mulatto woman. Smith and Drake[8] discuss a similar case. The scarcity of detailed reports such as these make it seem worth while to report the following account of the disease in three siblings of a negro family:

CASE REPORT

E. C., a twenty-one-year-old, single, Negro porter, from Carolina, was admitted to the Presbyterian Hospital January 23, 1946, with the complaint of pain in the left chest of two days' duration. His past history included rejection from the army because of "high blood pressure" which was discovered on routine examination. He had had no symptoms of hypertensive disease. Three years before admission he had had an attack of painless jaundice lasting about a week without change in the color of his urine. No history of exposure to occupational disease or injurious chemicals was elicited. There was no history of jaundice in other members of his family.

Physical examination revealed a muscular man in acute distress from pleuritic pain. His temperature was 101.8°F., pulse 88, respirations 20, and blood pressure 150/90 mm. Hg. The nose was moderately congested. Splinting of the left chest was apparent. There was a pleural rub with pericardial component in the third and fourth left intercostal spaces about 7 cm. from the midline. Moderate enlargement of cervical, axillary, epitrochlear and inguinal lymph nodes was noted. The remainder of the physical examination was within normal limits. The liver and spleen were not palpable. Icterus was not present.

A chest plate showed slight increase of density of the left costophrenic angle which was interpreted as pleurisy. An electrocardiogram demonstrated notching of QRS, left axis deviation and slight elevation of RT4F. Subsequently, the elevation of RT4F decreased. Later RT_1 became slightly elevated, T_1, T_2 and T4F increased in voltage and RT4F became elevated again. This was interpreted as compatible with the diagnosis of pericarditis. Sputum did not contain pneumococci or hemolytic streptococci; Streptococcus viridans predominated in culture. Nose and throat cultures were negative for hemolytic streptococci. The titer of cold agglutinins in the serum was found on admission to be 1:64, but it quickly fell to less than 1:4. The tuberculin test was positive in a dilution of 1:1000.

The white blood count on admission was 14,500 with 80 per cent neutrophiles. Throughout most of the patient's stay in the hospital the white blood count remained moderately elevated with a maximum of 18,000, and the differential showed a predominance of neutrophiles. Shortly before discharge the count fell to normal. At no time were abnormal lymphocytes to suggest infectious mononucleosis observed in the blood smear. There was an eosinophilia which reached a maximum of 15 per cent on the eighth hospital day and fell

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to 6 per cent at the time of discharge. Sheep red blood cell agglutinins were present in a dilution of 1:128 on admission. Determinations one week later showed titers of 1:32 and 1:64.

The Kline and Frei tests were negative. Urine examination was normal. Serum albumin was 4.6 Gm. per cent, globulin 3.4 Gm. per cent, and euglobulin .6 Gm. per cent. Giardia intestinalis cysts were recovered from the stool.

It was thought that the illness represented a non-bacterial respiratory infection of undetermined etiology. The significance of the transient elevation of the heterophile antibody titer and of the eosinophilia was not clear.

On the fifth hospital day slight icterus of the sclerae was noted. The serum bilirubin level was found to be 1.6 mg. per cent, and later 2.3 mg. per cent, indirect. The urine did not contain bile but the test for urobilinogen was strongly positive. The cephalin-cholesterol flocculation test of Hanger[9] was negative. The blood cholesterol was 132 mg. per cent, and the phosphatase 2.2 Bodansky units. Further studies showed that an anemia had now developed. The hemoglobin on admission had been 15 Gm. and the red blood cells 5.4 million; these fell at the peak of jaundice to 12 Gm. and 4.4 million, respectively. The reticulocyte count was now 9.0 per cent. The blood smear revealed that 16 per cent of the red cells had the appearance of spherical microcytes. Unfortunately, the smears taken on admission were not available for re-examination at this time. The mean cell diameter was found to be 6.6 micra, mean corpuscular volume 80 cubic micra, mean corpuscular hemoglobin 26 millimicra, and the mean corpuscular hemoglobin concentration was 33 per cent. The demonstration of increased fragility of the erythrocytes was of great interest. Hemolysis of the cells in saline began at a concentration of .575 per cent and was complete at .375 per cent, while the blood of a normal control showed hemolysis beginning only at .450 per cent and complete at .325 per cent. The test for sickling was negative. The difference between the erythrocyte sedimentation rates of oxygenated and reduced blood was 2 millimeters (Winsor and Burch's test for sickle cell anemia).[10]

TABLE I

FAMILY OF E. C.

Name	Relationship	Hgb. Gm.	RBC Million	MCD Micra	Retics. Per Cent	Serum Bilirubin Mg. Per Cent	Urine Urobilinogen	Fragility	Spherocytes Per Cent	Spleen	Sickling
E. C.	Patient	12.0	4.4	6.6	10.0	2.3	Increased	.575–.375	16	Palpable	Neg.
D. C.	Sister	11.5	3.0	6.9	16.1	2.0	Increased	.625–.375	15	Palpable	Neg.
R. C.	Sister	13.0	3.6	7.0	16.0	2.4	Increased	.525–.325	7	Neg.	Neg.
M. C.	Mother	....	...	...	0.5	...	.....	.450–.300	None	Neg.	
L. C.	Sister	....	...	...	0.5	...	.....	.425–.300	None	Neg.	
J. C.	Brother	....	...	...	0.8	...	.....	.450–.325	None	Neg.	
R. A.	Aunt	....	...	...	1.4	...	.....	.425–.300	None	Neg.	

The patient's icterus cleared in about a week and during this time his spleen tip became palpable. A flat plate of the abdomen showed the spleen to be slightly enlarged but revealed no shadows of gallbladder calculi. A gallbladder series showed a normally filling gallbladder without stones.

It would appear that the anemia that this patient had developed was a hemolytic one. As there was no history of exposure to any toxic agents likely to produce this condition, since the test for sickling was negative and there was increased erythrocyte fragility, it appeared that this patient might have congenital hemolytic jaundice. The possibility was also entertained that this might represent so-called "acquired" hemolytic jaundice. To clarify the point a study of his family was undertaken. The father was dead, but the mother, three sisters and a brother,

as well as a paternal aunt were examined. They knew of no jaundice in the family. All members of the family were deeply pigmented without obvious evidence of admixture of white blood. The results shown in Table 1 were obtained.

It is evident that two of the patient's sisters showed evidence of abnormally rapid blood destruction, as well as increase of red blood cell fragility and a high percentage of spherical microcytes. Moreover, one had a palpable spleen. These findings indicated that the patient and his sisters had, in all probability, congenital hemolytic jaundice.

Splenectomy was not performed at this time as the manifestations of the disease were mild. The patient was discharged on February 19, 1946, with the diagnosis of pleurisy and pericarditis of unknown etiology and congenital hemolytic jaundice.

COMMENT

To support the view that congenital hemolytic jaundice is rare in the negro we examined our clinic records. More than 10 per cent of the patients over a period of two decades have been colored. Although seventy-nine cases of spherocytic acholuric hemolytic jaundice with increased fragility of the erythrocytes have been seen here, only once before has the condition been encountered in the negro. This was in a mulatto woman with a six-year history of jaundice. Splenectomy was performed in 1925, whereupon the jaundice cleared and the red blood cell count rose. Perhaps this woman had congenital hemolytic jaundice but no study of the family was possible.

SUMMARY

1. The case of a twenty-one-year-old negro with typical hematological findings of congenital hemolytic jaundice is reported.

2. A study of the family disclosed latent hemolytic disease in two sisters.

3. Congenital hemolytic jaundice appears to be rare in the negro.

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Review

Cretinism*

Part I—Definition, Classification and Etiology—A Review

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CRETINISM is a term frequently applied to all forms of thyroid deficiency occurring in early life. In 1902, Pineles[1] classified cretinism as follows: (1) congenital athyreosis or sporadic cretinism, (2) infantile or childhood myxedema and (3) endemic cretinism. To this classification might be added cretinism with congenital goiter, the evidence for which will be presented later.

The purpose of this paper is to review the subject of cretinism not only from the standpoint of classification but also in the light of contemporary advances in the knowledge of thyroid physiology. We shall also report our observations on a series of cases of cretinism seen and treated at the Lahey Clinic (Part II).

CONGENITAL ATHYREOSIS, THYROAPLASIA OR SPORADIC CRETINISM

The establishment of this entity was based upon careful search for thyroid tissue in thyroid-deficient infants and children. The first case was described in 1850 by Curling[2] and later examples were reported by others.[3,4] Only a few follicles of thyroid tissue were found at the base of the tongue or either side of the larynx in cases of cretinism described by MacCallum,[5] de Quervain and Wegelin.[6]

The etiology of this condition is thought to be a defect in embryologic development rather than the effect of some disease process in utero. That this defect is not the result of deficient pituitary influence is attested by the enlargement of the hypophyses in these cases. From a clinical point of view it would make little difference whether or not the fetus failed to develop a thyroid or whether the thyroid was destroyed in utero by goitrogenic agents, or, as has been suggested, by the presence in the mother of chronic alcoholism, tuberculosis, syphilis or other infectious diseases.[7] These infants often appear normal at birth, and in such cases external changes may not be detected until several months have passed. Such an embryologic defect should not be considered unusual, as other congenital endocrine anomalies do occur. Further discussion of this subject along with the maternal-fetal relationship and its bearing on cretinism will appear at a later date.

INFANTILE AND CHILDHOOD MYXEDEMA

Infantile myxedema may manifest itself very early in infancy, thereby making a clear-cut division between thyroaplasia and infantile myxedema difficult unless *x*-rays demonstrate fetal bone age. In general, the latter is milder and more insidious in onset. Thus, in severe forms of myxedema dating back to early infancy, it is obvious that the only possible method of distinguishing between this and congenital athyreosis would

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be by actual histologic study. When the thyroid gland can be palpated in the infant, the chances are that it is not a normal sized gland and must, therefore, be considered a goiter; in any event it excludes thyroaplasia. The question then arises, how can one attempt to distinguish between the endemic type of goiter with cretinism and infantile or childhood myxedema?

ENDEMIC CRETINISM

A cretin with goiter who is born in a region where goiter is prevalent is obviously an endemic cretin. Likewise, a cretin without goiter who is born in the same region is usually considered an endemic cretin, in which the thyroid has undergone degenerative changes incapable of regeneration. Such cases occurring outside a goiter belt would be considered examples of congenital athyreosis or infantile myxedema. On the other hand, isolated examples of cretinism with goiter are found outside of goiter belts; occasionally several members of the same family are similarly affected, thus the term congenital goiter. Histologically, congenital goiter is apparently indistinguishable from endemic goiter so that we have made no attempt to differentiate them clinically, except as suggested by the history. It must be admitted that the causes of endemic goiter cannot be excluded in many such cases.

Certain objections have been made to the thesis that endemic and sporadic cretinism are of the same secondary etiology, namely, thyroid deficiency. These objections were listed by Falta[8] as follows: First, the beneficial action of desiccated thyroid was not as constant in the treatment of the endemic as in the sporadic cretin; second, thyroid deficiency was not as pronounced in the endemic type of cretin; third, the clinical manifestations of the disease in the endemic cretin are more manifold than in the sporadic type; and lastly, deficiency in growth was delayed in the endemic and almost at a standstill in the sporadic cretin. De Quervain[6] reports that 80 to 90 per cent of myxedematous children are retarded in skeletal development whereas only 25 per cent of cretins with goiter and 50 per cent of cretins without goiter are so affected.

Endemic cretinism is associated with various central nervous system defects such as an occasional speech defect, deafness or deaf-mutism, which some believe is due in part to incomplete ossification of the stapes and incomplete formation of the ductus cochleae.[8] Deafness may occur in acquired myxedema in the adult; therefore, it is not surprising that during fetal life or infancy serious injury may result to the central nervous system and the cortical centers may fail to develop, although de Quervain and Wegelin[6] do not believe that an adequate explanation of these changes exists in endemic cretinism. In endemic regions, 29 per cent of cretins are deaf-mutes and 32 per cent are hard of hearing.[8] Feeblemindedness is also frequent. An associated parathyroid deficiency is not uncommon in endemic cretinism in India.

Falta's objections, made many years ago, are more readily explained today with the exception of the more extensive manifestations of endemic cretinism as compared to the sporadic type. Even these phenomena ultimately may be traced to inadequate nutrition or by the use of known goitrogenic agents in animals.

ETIOLOGY OF ENDEMIC GOITER

In a search for the etiology of endemic cretinism the causes of endemic goiter must be considered. Iodine deficiency has long been designated the most likely cause of endemic goiter. It is known, however, that an absolute insufficiency of iodine is not always present in endemic goiter regions since the iodine content of the water and soil may be high.[9] The iodine content of

the thyroid gland of children in these regions is low which, added to the frequent evidence of thyroid deficiency, points logically to an inadequate utilization or absorption of iodine.

McCarrison[10] showed that goiter disappeared from districts when a new supply of water was substituted even though the iodine content of the new water was lower than the former. Marine[11] originally pointed out that the need for more thyroid hormone in the body at critical times such as during puberty, pregnancy, menopause, infection or dietary excesses or deficiencies may exhaust the thyroid gland of iodine, especially if the intake or the availability of body iodine is insufficient. Other causes besides inadequate iodine in food or water have long been considered and referred to as "goiter noxae."

In McCarrison's[10] earlier contributions, he believed that endemic goiter was due to an "unsanitary condition" associated with intestinal infection, and he demonstrated that goiter could be prevented and cured by the administration of thymol. Similarly, Marine and Lenhart[12] showed that goiter in brook trout raised in hatcheries may be prevented by the addition of iodine. Gaylord and Marsh[13] were able to prevent goiter in brook trout not only by iodine but by arsenic and mercury in proportions which would be unlikely to kill bacteria. Thymol was ineffective. Scrapings from the wooden troughs caused goiter readily, strongly suggesting an infective agent or "goitrogenic colloid." McCarrison[10] produced a goiter in himself by oral administration of a fecal Berkfeld filtrate proving in this case at least a "goiter noxa." Crotti[14] has isolated a fungus from goiter as well as cabbage and believes this is a causative factor; his work apparently has not been confirmed. In McCarrison's[15] later work, he showed that various factors constituted the "unsanitary condition," first of which was a faulty diet containing either excess fat, fatty acids, lime or a deficiency of iodine. Deficiencies in vitamins A, B and C were also thought to play a part, although Spence[16] concluded otherwise. McCarrison also demonstrated, as have others, that an excess of such foods as bran, cabbage, ground nuts, maize, excess protein or meat could produce goiter in animals. Leathem,[17] on the other hand, was unable to produce goiter in rats on a high protein diet. McCarrison further stated that milk could prevent goiter under the above circumstances, and that thyroxin prevented cabbage goiter. Chesney, Clawson and Webster[18] demonstrated the strongly goitrogenic properties of cabbage, later thought to be due to organic cyanides by Marine,[16,19] although this has not been proved. Curiously, an antigoitrogenic substance has been found in cabbage, as well as in fresh alfalfa, lawn grass and oats. The accidental discovery of the goitrogenic effects of sulfaguanidine by Mackenzie, Mackenzie and McCollum[20] may be considered epochal in the history of the study of goiter since it led to the search for more effective antithyroid substances. As a result, Astwood introduced thiouracil which has proved suitable for clinical use. He also demonstrated the anti-

TABLE 1

Usual Findings in Thyroid Deficient Child	*Changes from Treatment with Thyroid or Spontaneous Return of Thyroid Function*
Retarded height age	Height age usually remains behind chronological age
Retarded bone age (more marked than height age)	Bone age approaches chronological age
Retarded mental age	Mental age remains behind chronological age
Sluggish mentality (and hypokinesis)	Mental activity approaches normal
Normal dental age by *x*-ray. Deciduous teeth remain	Normal dental age by *x*-ray. Expulsion of deciduous teeth
Enlarged sella	No change or increase in size of sella
High blood cholesterol	Blood cholesterol approaches normal

goitrogenic effect of iodine and thyroid substance on giving sulfonamides to rats.[21]

The widespread success in the use of iodine in the prevention of goiter, as introduced by Marine and Kimball,[22] does not in itself prove that deficient iodine intake is the sole cause of endemic goiter. The same conclusion was reached by McCarrison.[10,15] Wegelin[6] and McCarrison[10,15] both noted that wild rats in endemic goiter regions were non-goitrous, whereas goiters developed in their laboratory rats presumably from an unhygienic environment. Even individual human dwellings have been thought to be goitrogenic.[15] Other goitrogenic agents have been considered, such as increased calcium content of drinking water,[23] radioactivity[24,25] of soil and arsenic.[26] It is well known that thiouracil, thiourea derivatives, thiocyanates, cyanides, sulfonamides and promizole are goitrogenic agents; undoubtedly others will be found.[27–32]

The exact mode of action of all these agents is still not completely understood. As mentioned above, infection of the intestinal tract, aided by abnormal diets, may prevent the absorption of iodine. It is now known that many of the goitrogenic agents act directly on the thyroid gland, some preventing the absorption of iodine in varying degrees, others interfering with the manufacture of thyroid hormone, even if iodine is absorbed by the gland.[33] Whitehead[34] could not demonstrate that rape seed diets producing goiter in rats prevented the utilization of thyroxin by the tissues. Jandorf and Williams[35] in rat tissue respiration studies showed that thiouracil prevented increased metabolism of liver and muscle produced by thyrotropic hormone. Some believe that thiouracil has a tissue depressing action which contributes to its clinical effect.[36] That it may act on certain tissues in this way is evidenced by the complications which occur with thiouracil treatment of toxic goiter; although some of these complications, if not the majority, appear to be due to hypersensitivity since most of the reactions follow the criteria of any drug sensitization.[37]

In summary, it may be said that endemic goiter appears to be the result of: (1) inadequate intake of iodine; (2) inadequate bodily absorption of iodine; (3) inability of the thyroid gland to take up available iodine, or (4) inability of the thyroid gland to synthesize or discharge thyroid hormone.

Many known and undoubtedly many unknown circumstances or agents are responsible for such interference in iodine metabolism.

PITUITARY-THYROID RELATIONSHIP

Removal of the thyroid in the rabbit causes pituitary enlargement, as shown by Rogowitsch.[38] Marine[11] pointed out that the younger the animal, the greater the change. In 1851, Nièpce[39] discovered that the pituitary may enlarge four times its normal size in cretins. Schönemann's[40] work revealed a larger pituitary in all endemic goiter patients who were not apparently thyroid deficient. (Only in one case which he described as a cretin with goiter was a small pituitary found.) De Quervain and Wegelin[6] found that enlargement of the pituitary is the rule in endemic cretinism. MacCallum[5] and de Quervain and Wegelin[6] reported enlarged pituitary glands in cases of congenital athyreosis. Our measurements of the sella appear to conform to these observations (to be published). Regardless of whether the pituitary enlarges or not, many observers but not all by any means find that in myxedema, or following thyroidectomy in animals, or subtotal thyroidectomies in humans, there is an increased functional activity of the pituitary as shown by the finding of urinary thyrotropic hormone,[41–44] just as there is an increase in the urinary gonadotropins following castra-

tion, surgical or otherwise. This has also been demonstrated in rats in which goiter was produced by means of thiourea.[45]

Beginning with Rogowitsch,[38] several investigators demonstrated histologic changes in the pituitary following thyroidectomy. These changes consist largely in an increase of basophilic cells, vacuolization of cells,[46] a decrease in the acidophilic cells[47,48] and an increase in acidophilic colloid.[49,50] Griesbach and Purves[51] investigated the thyrotropic content of the pituitary following thyroidectomy in rats and demonstrated that the thyrotropic content was diminished in proportion to the decrease in acidophilic cells, but at the same time the thyrotropic hormonal content was increased in the blood serum. In other words, thyroidectomy increased the thyrotropic hormone output but at the same time decreased the amount in the pituitary gland. The same changes took place in animals fed rape seed diets which produce goiter. They concluded that thyroid hyperplasia produced by the goitrogenic agent is secondary to impairment of thyroid hormone synthesis, which in turn stimulates the output of the pituitary thyrotropic hormone. Mackenzie and Mackenzie[52] observed similar results with sulfaguanidine. Reveno[53] reported an increase in basophilic cells and a slight increase in pituitary weight in a patient with thyrotoxicosis, who was given a total of 178 Gm. of thiouracil over 381 days.

Iodine which prevents goiter should also prevent pituitary changes, at least to some degree. Loeser,[54] on administering iodine to normal rats, found an increase in thyrotropic hormone content of the pituitary. Evans and Simpson[55] fed normal rats fresh beef thyroid, which caused an appreciable decrease in the weight of the pituitary. Marine et al.,[56] in an experiment on rabbits, concluded that thyroxin is capable of preventing hypertrophy of the pituitary after thyroidectomy and in parenchymatous goiter, with restoration of the pituitaries to normal. Iodine under the same conditions was effective only in the latter. It is evident then that the acidophilic cells may decrease with decreased functional activity of the thyroid and vice versa.

Zeckwer et al.[49] suggested that the stunting of growth in the cretin rat might be due to a decrease in acidophilic cells. Of interest was their observation of crossing a cretin male rat with a cretin female rat, following which a "normal" litter was born. The pituitary of the cretin mother rat contained numerous acidophilic cells suggesting to these authors the stimulating or sustaining influence of the fetal thyroid hormone. Flower and Evans[57] were able to maintain normal growth in thyroidectomized rats with pituitary growth hormone. Salmon,[58] on the other hand, was not able to stimulate growth with pituitary growth hormone in thyroid-parathyroidectomized rats unless a thyroid remnant was left behind, but thyroidectomy was performed at birth in contrast to operation at a later date in the preceding work. Scow and Marx,[59] however, were able to produce 100 per cent increase in growth in thyroidectomized rats with growth hormone.

Remington[60] found that the retarded growth of rats fed a goiter-producing diet could be prevented on an iodine-free diet containing 2 per cent dried pig liver. He concluded that while liver produces increased hyperplasia, there must be some substance contained therein aside from the vitamin B content, which stimulates the thyroid and maintains growth. One would have to conclude, therefore, that thyroid hormone production was adequate or that some other mechanism in combination with small amounts of thyroid hormone is evoked to maintain growth.

Since it is believed that growth hormone arises in the acidophilic cells, the suggestion of Zeckwer et al.[49] is attractive and arouses

curiosity as to the acidophilic cell count in the occasional excessive growth of children with hyperthyroidism. When Williams et al.[61] combined thiouracil and growth hormone in rats, there appeared to be some restriction of the effect of growth hormone, suggesting interference with the action of the latter on the tissues in general (vide supra).

In summary, there is general agreement that thyroidectomy and goitrogenic agents produce: (1) enlargement of the pituitary, and (2) a change in the acidophilic and basophilic ratio. There is not unanimous agreement regarding the increase of thyrotropic hormone in blood and urine under such circumstances, but it would appear that the weight of the evidence points to an increase. These changes may be prevented under a variety of circumstances by the administration of antigoitrogenic agents such as iodine, desiccated thyroid, thyroxin, diiodotyrosine, high meat intake and/or an adequate diet.

In view of the previous discussion concerning goitrogenic agents and their effect on the pituitary-thyroid mechanism, it is important to emphasize here, lest it be overlooked, that insufficiency of iodine intake alone will produce the same changes in the thyroid and pituitary as goitrogenic agents. Apparently, in rats at least, the thyroid will respond to iodine lack after hypophysectomy, but at a much lower level, an observation of possible importance in early fetal life.[62]

MECHANISM OF PRODUCTION OF GOITER

Marine[63] suggested that colloid goiter, which is a step in the development of nodular goiter, was a result of alternating hyperplasia and involution. The cycle may be postulated as follows: The goitrogenic agent blocks, at least in part, the take-up of iodine by the thyroid cells, so that formation of the thyroid hormone is eventually decreased. There is a difference of opinion in this regard, some finding no restriction of iodine take-up,[64,65] while others do,[66,67] a difference which in part is due to variable goitrogenic agents as well as the species of animals used in the experimental work.

All such work must be interpreted with these reservations in mind. In the human there is no doubt that the thyroid absorbs iodine while on thiouracil treatment, but observations in this Clinic indicate that iodine absorption is inversely related to the degree of thiouracil effect, and that when the state of myxedema has been produced very small amounts of iodine are to be found in the gland.[68] Here, however, we are dealing with a hyperactive gland to start with whereas most animal experiments are on subjects with normal glands. Barker[69] gave thiouracil to rats and then either desiccated thyroid or thyrotropic hormone. He concluded after studying the effect on the basal metabolic rate that thiouracil depresses the production of thyroid hormone. This decrease in thyroid hormone output results in excess pituitary thyrotropic hormone which, in turn, causes hyperplasia of the thyroid cells. If the goitrogenic agent is continuous and increasing in its effect, it will eventually block all iodine absorption by the gland, or completely prevent thyroid hormone production, following which myxedema ensues. A state of continued hyperplasia, exhaustion and eventually atrophy might take place in such cases. On the other hand, it is likely that the action of goitrogenic agents might be intermittent or that there are intervals when more iodine is available for the thyroid, allowing for temporary manufacture of effective thyroid hormone. This would result in two changes: first, to decrease the stimulus to the pituitary, thereby reducing the thyrotropic hormone output; and second, to cause

partial involution of the thyroid gland with colloid storage.

Hyperplasia of the thyroid cells does not mean increased thyroid hormone output. If sufficient iodine is available, the hyperplastic cells take up iodine with great avidity, in some cases at least, and colloid storage takes place even though the output of thyroid hormone is increased thereby. The thyroid cells appear to have the ability to take up iodine and deposit it with colloid in the follicles, yet at the same time they also may remove colloid from follicles and secrete it as effective thyroid hormone into the blood stream. Once the thyroid cells are satiated with iodine and colloid is stored, their intrafollicular secretory activity is markedly reduced before, it seems reasonable to believe, the stored colloid can be as quickly converted to active thyroid hormone and discharged. The conversion of inactive colloid into active thyroid hormone within the follicle is thought to result from the secretion into the follicle of an enzyme capable of performing this synthesis.[65] Goitrogenic agents may depress this function,[70] and free iodine is thought by de Robertis and Nowinski[71] to do so. Thus, another rôle is assigned to the thyroid cell which by virtue of the decreased enzymic activity just mentioned aids in trapping the colloid present. This in turn may create a relative thyroid deficiency in the tissues, reinstituting the cycle of events just described.

The failure of the cells of some follicles to become hyperplastic again after being distended with colloid, which was low in effective thyroid hormone, is possibly the result of atrophy of the cells from the pressure of overdistention. It could also be postulated that the same cycle could be produced by intermittent demands of the tissues for excess thyroid secretion without the presence of a goitrogenic agent. By alternate feeding of cabbage and iodine to rabbits, Webster[72] was able to produce a nodular type of goiter such as is seen in human glands in endemic areas.

The prevention of these changes in the early stages by iodine implies that the effect produced by the goitrogenic agent is only partial, thus enabling absorption of some iodine or manufacture of thyroid hormone by the gland. The prevention of goiter by thyroid or thyroxin could take place by supplying the tissue demands for active thyroid hormone, but at the same time inhibiting the pituitary directly or by the breakdown of the iodoproteins in the tissues, yielding available iodine for the adequate production of thyroid hormone in the gland.

Perkin[73] has noted that on incubating blood taken from individuals with long-standing hyperthyroidism, the organic iodides are rapidly broken down. This phenomenon he interprets as evidence for the existence of an enzyme which by breaking down organic iodides, renders available inorganic iodides for the depleted thyroid, and hence resynthesis of thyroid hormone.

The reduction in the size of endemic goiter in humans and animals on giving desiccated thyroid or thyroxin has been noted by several writers.[63,74] We have observed it particularly in individuals with goiter and concurrent thyroid deficiency. Hyperplasia or fetal adenomas are frequently found in cases of cretinism with goiter. Involution of such areas is probably the mechanism in the reduction of the size of the goiter by desiccated thyroid. It is obvious that degenerated colloid adenomas cannot react in this manner. Supplying the tissues with necessary thyroid hormone relieves the stimulus to pituitary thyrotropic hormone production, thus causing regression; but another possibility arises from the unconfirmed work of Reforzo Membrives[75] which demonstrated that the pituitary of an animal which has been given thyroid is capable of depressing metabolism when

transplanted into the peritoneum of a normal animal. Lerman[76] (quoted by Means) gave iodine to a myxedematous boy with adenomatous goiter and noted improvement in the myxedema with a temporary rise in the basal metabolic rate to normal. Further observations could not be made. A similar effect was regularly noted by Webster and Chesney[77] in administering iodine to rabbits made goitrous by cabbage. Hurxthal and Greene[78] noted no change on giving potassium iodide to thyroid-deficient children with colloid adenomatous goiter or without goiter.

Following surgical removal of adenomatous goiters there may be a decrease in thyroid hormone output, which in turn stimulates the pituitary and produces hyperplasia as well as hypertrophy in the remaining thyroid tissue and eventually possible recurrence of goiter. In one case (number 21) under our observation, a recurrence took place after operation, and the gland diminished in size by the administration of thyroxin, the patient being thyroid deficient. In another of our cretins (Case 31) the removal of the goiter without concurrent thyroid deficiency was followed some years later by recurrence of goiter with hyperthyroidism and a spurt in growth occurring a few years after desiccated thyroid had been discontinued. The transition from thyroid deficiency to hyperthyroidism in cretins with goiter may take place spontaneously as will be demonstrated in Part II (Cases 31, 32 and 33).

It has been reported that myxedema has been relieved by removal of large adenomatous goiters.[79,80,81] A possible explanation of this is that the normal thyroid tissue is so compressed by the overdistended colloid adenomas that little or no thyroid function exists. In such cases the mechanism for the stimulation of thyroid function existed before removal of goiter, but was unable to operate.

Part II—Observations and Treatment of Cretins Having Concurrent Hypothyroidism, Euthyroidism or Hyperthyroidism

Thirty-five cases of cretinism have been seen at the Lahey Clinic of which twenty have been followed for various intervals during their growth period and their progress under treatment has been observed by one of us (L. M. H.).

We have classified these cases under two headings: those without obvious goiter, of which there were eighteen; and those with palpable thyroid glands or obvious goiter, of which there were seventeen.

In many of the cases of cretins without goiter the deficiency was noted in early infancy. (Fig. 4.) Lacking histologic proof, they cannot be diagnosed definitely as thyroaplasia, but there is little doubt that some fell into this group. Case 7 was one of twins (fraternal); two placentas were known to have existed so that there is little question that this case could be so identified since the other twin was normal. In general, the bone age and height age were more retarded in the group without goiter, in which there was no instance of recovery of thyroid function. Results of treatment in this group were on the whole as good as in the group with goiter.

In cretins with goiter or palpable thyroid glands, as was stated in Part I of this report, the level of thyroid activity may eventually become normal or actually increase to a state of hyperthyroidism. The result of this change of function is parallel to the results obtained by feeding desiccated thyroid to untreated cretins. (Table I and Fig. 1.)

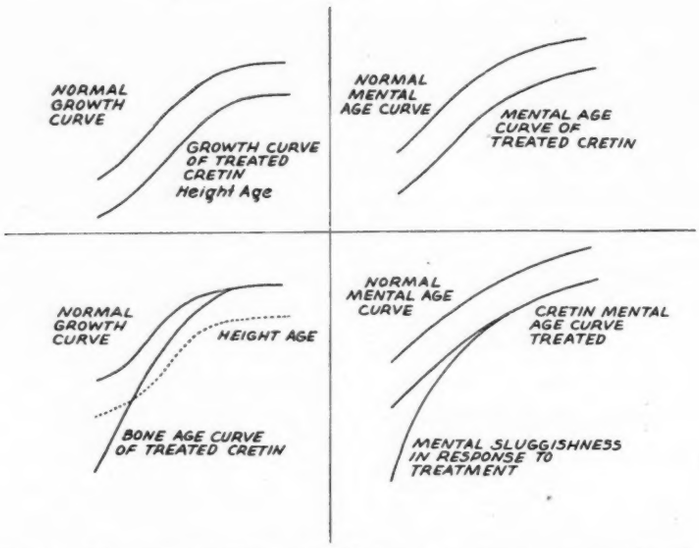


FIG. 1. *Diagrammatic illustration of effect of treatment or resumption of normal thyroid function in cretins. The theoretical relationships between height age, bone age, mental age and mental activity are shown.*

In considering children with goiter, including those who have never been thyroid deficient, the following classification helps to clarify their status as regards thyroid function, past or present:

Group I. Normal children with endemic goiter and euthyroidism (Cases 34 and 35).

Group II. Normal child with endemic goiter and hyperthyroidism (Case 34 possibly).

Group III. Cretins with goiter and concurrent thyroid deficiency (myxedema) (Cases 19 to 26 inclusive, Figs. 2, 8 and 10).

Group IV. Cretins with goiter, antecedent thyroid deficiency and concurrent euthyroidism (Cases 27 to 30 inclusive, Fig. 6).

Group V. Cretins with goiter, antecedent deficiency and concurrent hyperthyroidism (Cases 31 to 33 inclusive, Fig. 7).

Of seventeen cases of cretinism with goiter or palpable thyroid glands, eight fall in Group III as listed above, four in Group IV and three in Group V. Cases in Groups I and II, although not cretins, are included by way of comparison since they were brothers of cretins: Case 34, brother of Case 29, listed in Table IIIB; Case 35, brother of Case 33, listed in Table IIIC, and therefore of the same etiology.

Of all cases with goiter, five were known to have had goiter at birth (Cases 21, 31, 32, 33 and 35). Two were brothers born in Nova Scotia in a locality where goiter was not endemic. Their mother was examined and showed no signs of thyroid deficiency nor did she have a goiter. Three others had no family history of goiter and were born in New Hampshire or Massachusetts. Of those who had goiter appearing in infancy, two were from a family of five children, four of whom had a goiter. The father and mother were without goiter. Two of the others in this group of five known to have goiter at birth were brothers, one a typical cretin, and the other with apparently normal thyroid function. These cases along with evidence presented in the previous pages supply the reasons for use of the term, congenital goiter.

Three cretins with goiter developed hyperthyroidism (Table IIIC) and were operated upon. One patient was operated upon twice, once in a euthyroid state and later

in a hyperthyroid state as previously mentioned (Case 31). Two of these cases were described elsewhere by Bartels[82] (Cases 31 and 32). The third case is shown in Figure 7 (Case 33). All of these patients had retarded skeletal as well as mental development. Skeletal retardation as shown by bone and height age was present in all others with concurrent thyroid deficiency and in some who were in a euthyroid state, indicating past deficiency (Cases 27, 28, 29 and 30).

Many of the characteristic changes of thyroid deficiency are found chiefly in advanced cases, especially those without goiter. The so-called "monkey face" results partly at least from failure of development of the middle fossa (spheno-occipital synchondrosis), causing a shortening in the length of the skull from the root of the nose to the base. (Undoubtedly other sutures are also involved.) This persists to some degree, depending largely upon the time when treatment was begun. Late closure of the fontanels goes hand in hand with delayed osseous development. Dental age as judged by clinical inspection appears to be delayed, largely because the deciduous teeth are retained longer even though the permanent teeth are erupting.[83,84] If roentgenograms were used to judge dental age by the appearance of the six, twelve and eighteen-year old molars, there is little variation from the normal except perhaps in untreated cases of long standing.

The extent to which bone age, as determined by the hand-wrist roentgenograms* lagged behind the chronologic age, was dependent on the duration of the disorder as well as the amount of previous treatment. A disproportion between the length and width of the long bones resulting in the short stubby hands is found chiefly in untreated cases of long standing. (Fig. 5.) In severe cretinism osteochondritis is not uncommon.[85] It was rarely observed in our cases although roentgenograms of the whole skeleton were made in only a few. None presented any signs or symptoms referable to such changes.

The dry skin, the fine and often sparse hair, the bloating and pallor about the eyes are all present in some degree if thyroid deficiency is present. In two cases (14 and 16) excess hair was present. One of these has not been seen since treatment was started; the other patient lost most of the body hair, particularly on the back where it was present in typical swirls, and on the arms and legs, as well as some on the face. (Fig. 12.) Excess hair growth has been reported in a case of cretinism[86] and we have seen one such case in adult myxedema[87] whose excess hair disappeared on treatment with desiccated thyroid. An enlarged tongue is often present and may be one of the earliest signs in very young infants when appraisal of growth and other signs is not possible (Case 19). Enlargement of the thyroid should naturally direct attention to the question of adequate thyroid function. The enlargement may be so great at birth as to cause strangulation.[8] Goiter of the lingual thyroid may be present. Pot-belly and occasionally umbilical hernias are found. When the function of the thyroid returns in cretins with goiter, there may be no evidence of concurrent myxedema as shown by the above signs, including the blood cholesterol value or the basal metabolic rate. The bony changes, however, persist including retardation of height† and mental age although the child may appear alert and even hyperthyroid. In rare cases of comparatively short duration, the usual sluggish mental reaction may be absent even with marked deficiency (Cases 11 and 20).

It is difficult to propose an all-inclusive plan for the diagnosis of early thyroid deficiency. At birth goitrous infants even if stillborn may be of normal size. This may

* Todd's standards used in all cases.

† Height age calculated from Burgess growth charts.

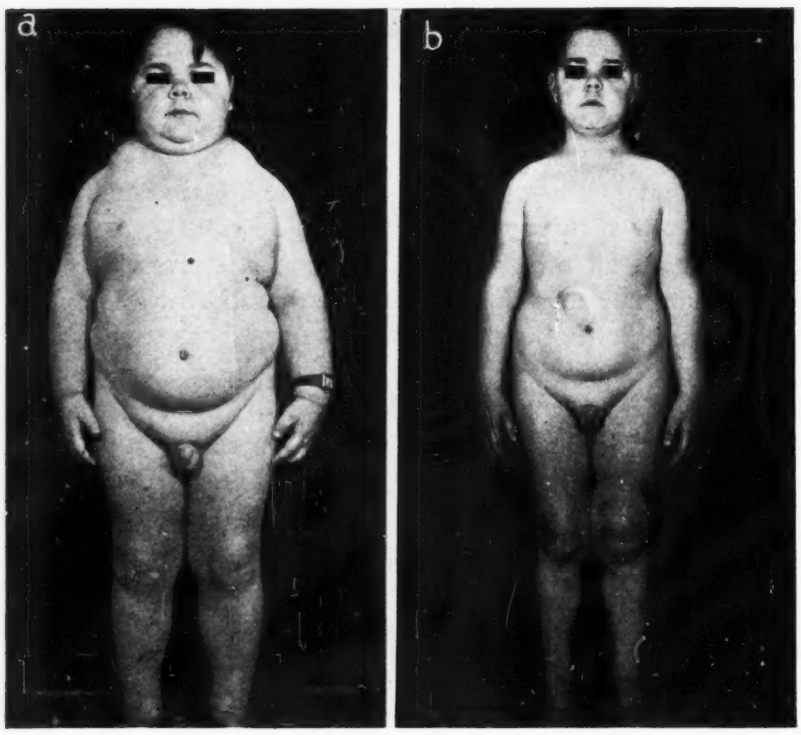


FIG. 2. (*Case* 23.) *a, cretin, age fourteen, with substernal goiter (congenital) and concurrent thyroid deficiency before treatment. Basal metabolic rate,* −36 *per cent; blood cholesterol,* 360 *mg. per* 100 *cc. b, after fourteen months' treatment.*

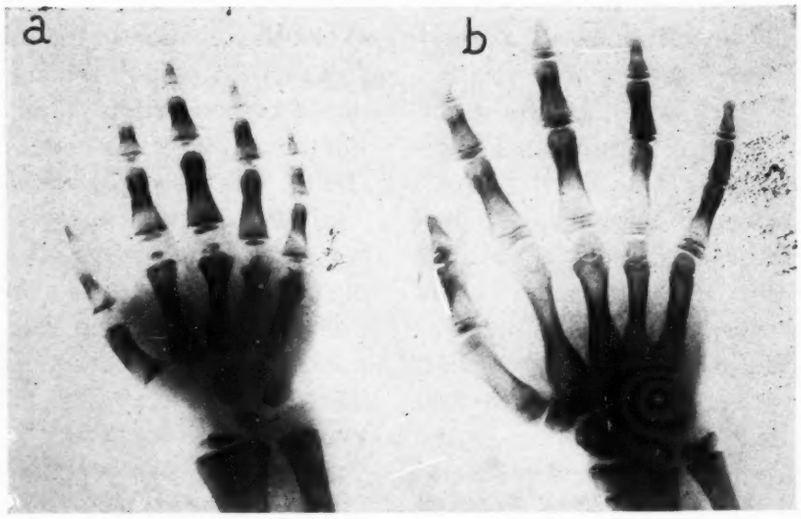
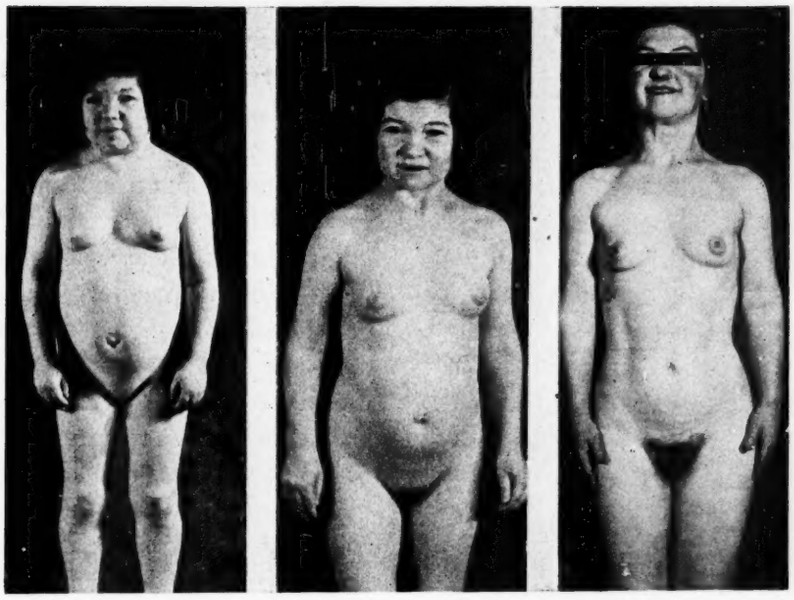


FIG. 3. (*Case* 23.) *a, bone age four years and height age seven years at beginning of treatment; b, fourteen months later, bone age eleven years and height age nine years, illustrating a more rapid increase in bone age than in height age.*



A B C

FIG. 4. (*Case* 5.) *Cretin, age eighteen. Irregularly and inadequately treated; onset in infancy; no palpable thyroid; presumably congenital athyreosis.* A, *before institution of adequate therapy. Basal metabolic rate* −18 *per cent; blood cholesterol* 430 *mg. per* 100 *cc.; bone age, eleven and one-fourth years.* B, *after three months of treatment;* 10 *gr. of desiccated thyroid per week.* C, *after one year of treatment. Height* 49½ *inches at eighteen; two years later,* 53½ *inches. For bone changes see Figure* 5.

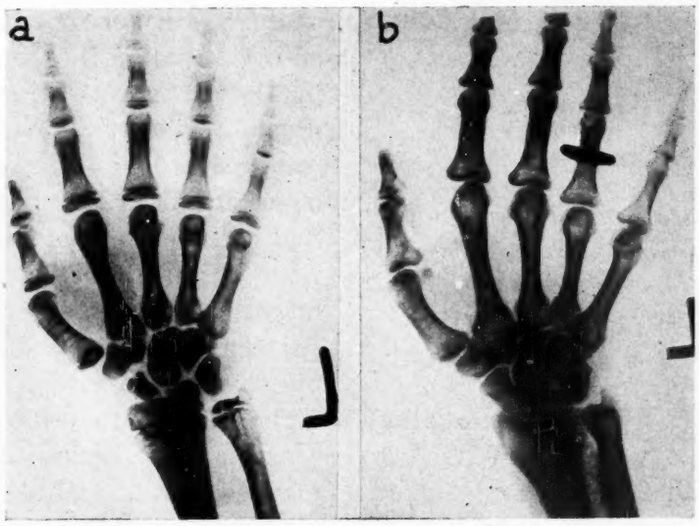


FIG. 5. (*Case* 5.) *a, roentgenogram of hand of cretin eighteen years old with concurrent thyroid deficiency in which previous treatment was inadequate. b, after three years of treatment resulting in complete epiphyseal closure. Note dense and widened phalangeal bones due to long-standing hypothyroidism. Height age at eighteen years was eight years; at twenty, ten years. Puberty began during the first year of treatment* (*see Fig.* 4).

FIG. 6. (*Case* 27.) *Goitrous cretin with antecedent thyroid deficiency and concurrent euthyroidism; onset at two years. At age fourteen, height age eleven and one-fourth, bone age eleven; change in thyroid function at eleven years with growth spurt and further enlargement of goiter; basal metabolic rate* ±0 *to* −10; *blood cholesterol* 160 *mg. per* 100 *cc.*

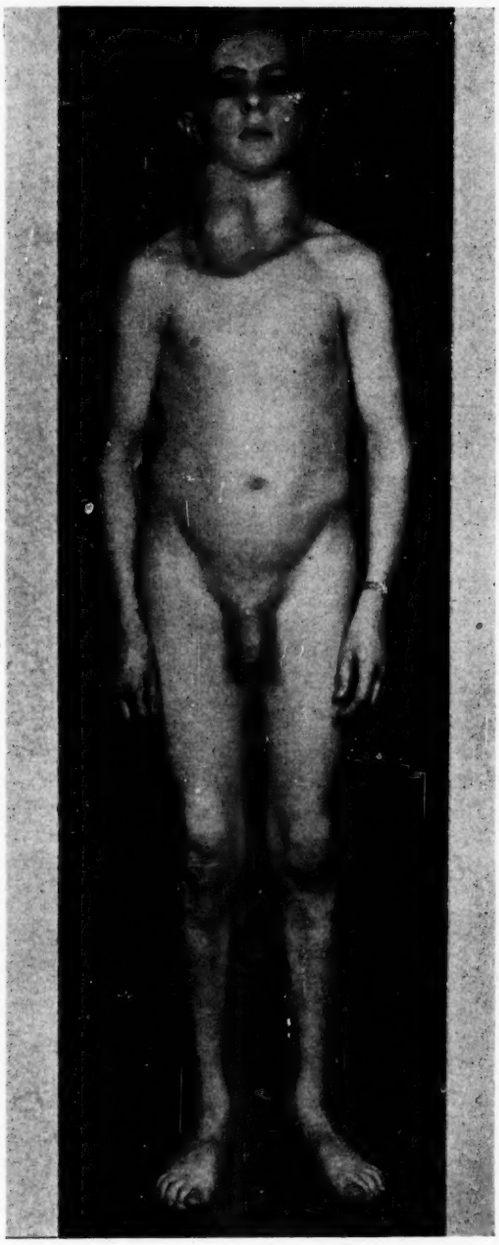
also be true of thyroaplasia.[88] Retardation of growth and mental development, the two most important clinical features, should attract attention. Even before this can be ascertained, cretinism may be suspected in infants who fail to nurse well and make the usual progress in the first weeks or months of life. These signs, however, may be present and due to other conditions. When other features of thyroid deficiency as enumerated above are present, the disorder has existed for at least several years and usually indicates a marked thyroid deficiency.

The most common causes of retarded growth are: mongolism, pituitary dwarfism, cerebral injury, nutritional deficiency, congenital heart disease, achondroplasia, Laurence-Moon-Biedl and Turner's syndrome or allied syndromes. Bone age is retarded in many of these but not to the same extent found in thyroid deficiency, with the possible exception of pituitary dwarfism. In our experience, bone age determinations have been of great value in the diagnosis of thyroid deficiency, especially in patients who have received inadequate treatment and in whom clinical evidence of myxedema has been eliminated in various degrees. The discrepancy between bone age and chronological age probably cannot be estimated closer than six months to one year with any assured accuracy, but it is seldom that we see a patient for the first time with thyroid deficiency of less than a year's duration, and therefore one usually finds a difference of three years or more between bone age and chronological age. As pointed out by Dorff,[89] more frequent roentgenograms should be taken at birth.

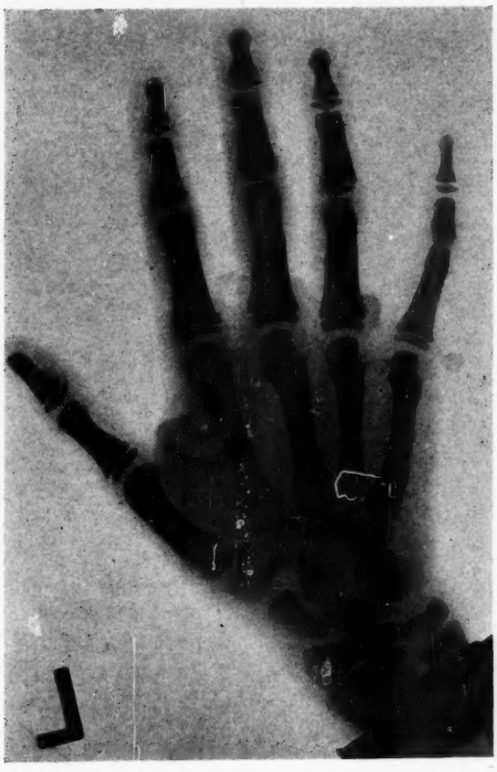
A frequent problem which arises is that of confirming a previous diagnosis of thyroid deficiency in a child without goiter in whom treatment has been adequate or sufficient to erase definite stigmas of cretinism. As stated previously, bone age may lag, but in treated cases the bone age may be fairly close to the chronological age and consequently a definite decision cannot be made on this finding alone. Little evidence of mental retardation may be present in some patients treated early so that one is confronted only with a child who appears normal except for retarded growth. A summary of the changes with treatment are shown in Table I. The history, of course,

is of great importance, but to be certain desiccated thyroid should be withheld for several months. A great rise in blood cholesterol within a month, together with clinical evidence of thyroid deficiency which may not appear for several months more, should settle the question. The presence of an enlarged sella would appear to add to the diagnosis of cretinism. In this connection, we disagree with Dunn[90] who considers such as indicating the pituitary as the primary cause.

Since metabolic studies are impractical in infancy, blood cholesterol determinations provide the most easily available laboratory test to confirm a possible diagnosis of thyroid deficiency. More elaborate studies can be carried out, such as estimations of blood iodine, blood phosphorus and phosphatase, creatine or creatinine excretion.[91–99] The clinical features of many disorders in which growth retardation is present are so characteristic (viz., mongolism, achondroplasia, Laurence-Moon-Biedl syndrome) that the laboratory investigation for diagnosis is scarcely indicated. Since the administration of thyroid when given in moderate doses is harmless in the young and because the



A



B

FIG. 7. A and B. (*Case* 33.) *Congenital goiter with antecedent thyroid deficiency and concurrent hyperthyroidism. At age eighteen, height age twelve years, bone age thirteen years; increase in size of goiter beginning at age sixteen with spurt in growth; increased activity of thyroid in the past two years caused the bone age, thirteen, to approximate the height age, twelve.*

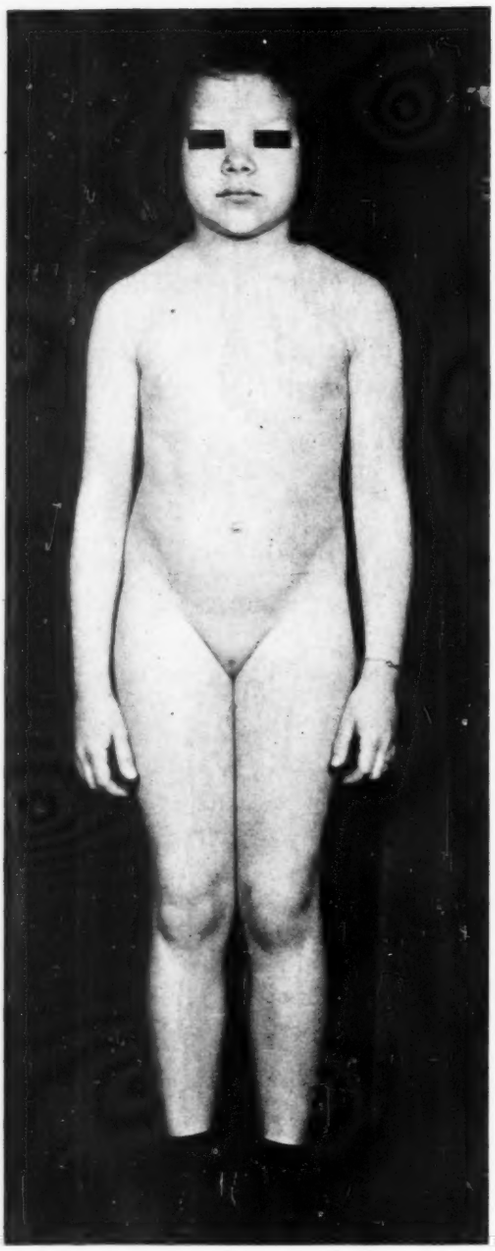


FIG. 8. (*Case* 20.) *Cretin with concurrent thyroid deficiency and a palpable thyroid gland of colloid type before treatment. Age eleven years, height age eight and one-half years; bone age seven and one-fourth years. Basal metabolic rate* −32 *per cent; blood cholesterol* 376 *mg. per* 100 *cc. There was no apparent retardation in mental age; the child was mentally alert.*

response to this medication is so striking in the thyroid-deficient child, the use of thyroid as a therapeutic test is indicated in case of doubt.

During the treatment of thyroid-deficient children with desiccated thyroid, it is to be noted from the charts that bone maturation apparently proceeds at a more rapid pace than height. One might believe that height age should increase proportionately, but even when growth is restored to normal rate, bone maturation takes place more quickly. (Fig. 3.) When this occurs even in early childhood, it suggests some other influence besides the direct effect of the thyroid itself (see Part I).

In hyperthyroidism in children on the other hand, the rate of growth apparently is parallel to the rate of bone maturation, which is more rapid than normal.

It will be further noted from the charts that those cases in which growth is completed were, in the majority, below normal height age. In no case did the growth rate definitely exceed the normal even if the patient was adequately treated. In an individual case the predestined height, i.e., the

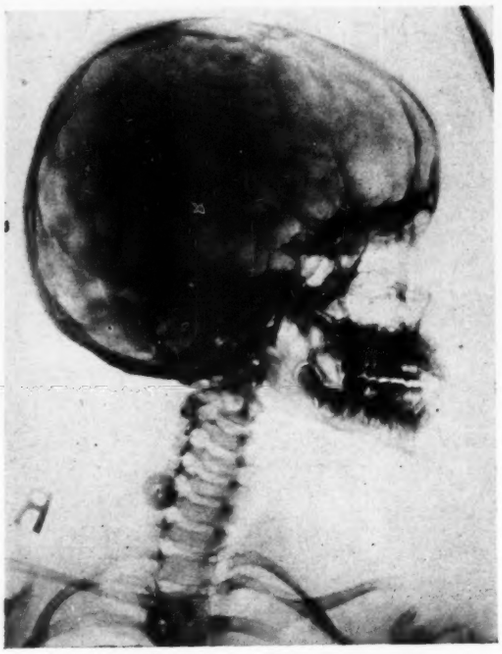
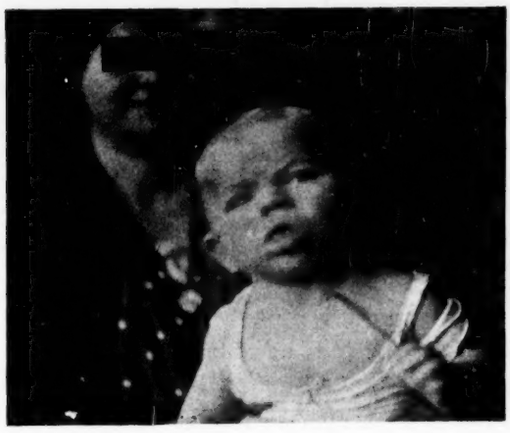
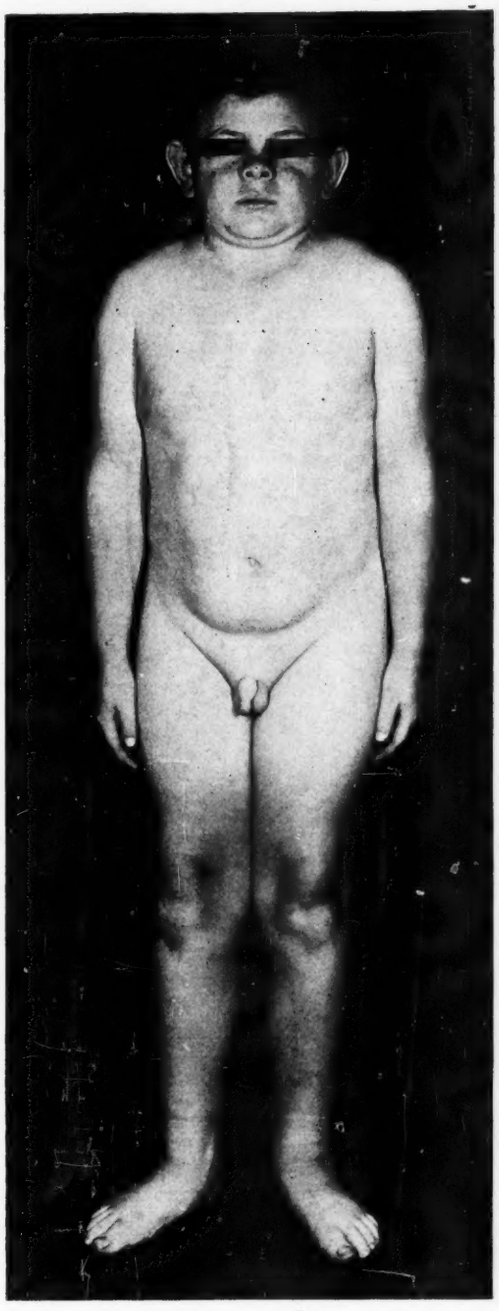


FIG. 9. (*Case* 20; *same case as shown in Fig.* 8.) *Skull of a cretin showing an enlarged sella. Sella measures* 11 *mm. deep and* 11 *mm. anteroposteriorly. Average normal measurements for this age are* 9.36 *by* 6.18 *mm.*

height which would have been reached had not thyroid deficiency occurred, cannot be known but only approximately surmised by obtaining the heights of other members of the family.

The question arises whether or not more intensive treatment in these cases might have eventually increased the final height. Since bone maturation increases at a greater speed than height, bone maturation would cause earlier cessation of growth. Particularly is this true in those individuals who have passed the usual age for puberty without treatment and in whom the administration of thyroid hastens puberty, at which time epiphyseal closure is accelerated. It appears, therefore, that the delay in growth caused by thyroid deficiency before treatment is started cannot be recovered. In other words, the ultimate height of a cretin on adequate therapy will be the height which he would have attained under normal conditions, minus the amount of growth





A B

FIG. 10. (*Case* 19.) A, *cretin with concurrent thyroid deficiency at twenty-one months, having begun at four months of age and necessitating gastrostomy because of dysphagia; thyroid palpable. Note adenomatous goiter in mother.* B, *same patient at twelve years. Treatment prior to admission (B. and W. thyroid ¼ gr. daily). Treatment thereafter was adequate in dosage but irregularly taken; idiocy.*

retardation which took place during the period of thyroid deficiency.

The mental age finally attained in these cases appears to be in proportion not only to the duration of the thyroid deficiency before adequate treatment, but also to the age at which it took place. In only three cases has a normal intelligence been attained

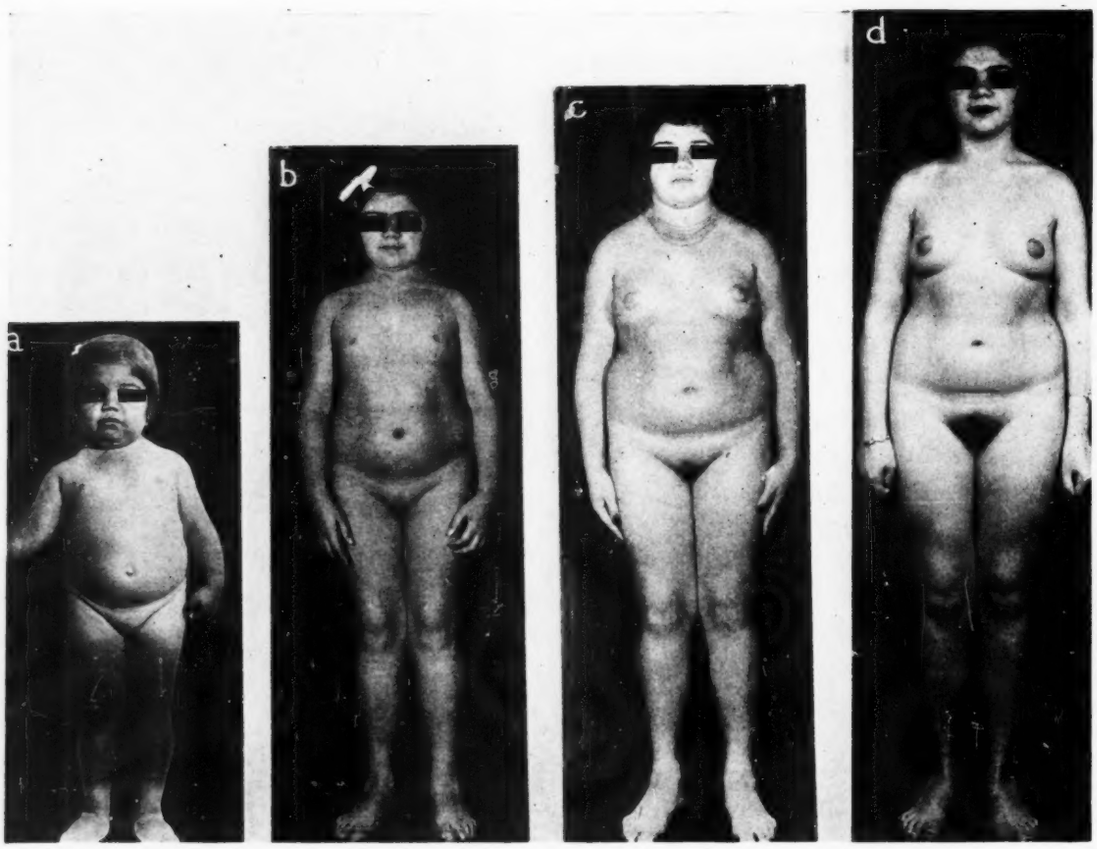


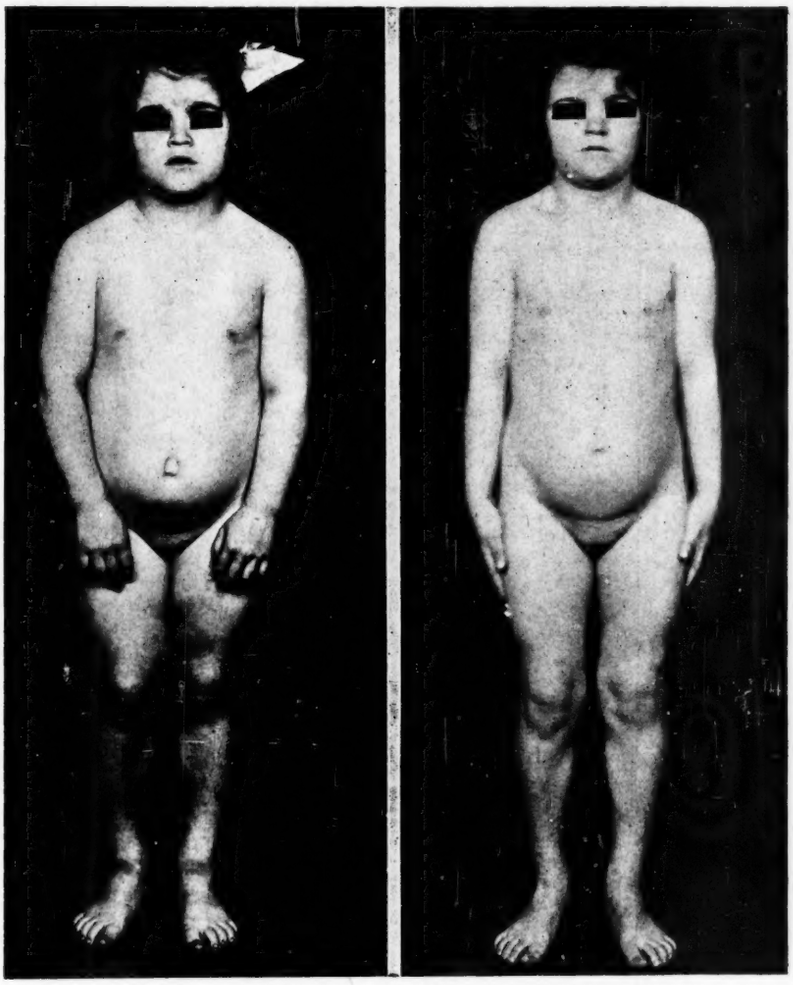
FIG. 11. (*Case 9.*) *Cretinism; adequate treatment after age of seven with excellent results; infantile myxedema or congenital athyreosis.*

	Chronological Age	Bone Age	Height Age
a	7 yr.	9 mo.	3½ yr.
b	12 yr.	7 yr.	8¼ yr.
c	16 yr.	12¼ yr.	11¼ yr.
d	18 yr.	15 yr.	12 yr.

At seven years of age the child was unable to walk unaided. Marked flat feet and lumbar lordosis. At age sixteen when picture was taken, the patient had not taken thyroid for some months; normal intelligence, height age retarded, radial epiphyses closed at eighteen years of age (see growth chart, Case 9). Sella measured 9 by 13 mm. at seven years and 11 by 14 mm. at eighteen years. Blood cholesterol when first observed, 460 mg. per 100 cc.; basal metabolic rate −26 per cent; bone age of nine months at seven years of age strongly indicates congenital athyreosis.

by those who reached the age of eighteen and in these cases adequate treatment was begun early. One patient (Case 18) now forty-five years old has taken thyroid since the age of three months; she may be considered a high grade moron but is able to carry on her duties as a wife and homemaker. Only one case can be considered to have idiocy; the remainder who have matured are able to earn their own living although it is doubtful that all could maintain themselves independently.

We believe that desiccated thyroid in doses of not less than 1 gr. per day in children from one to five should be attempted. The best guide to treatment is the tolerance



A B

FIG. 12. (*Case* 14.) *Cretin with concurrent thyroid deficiency and excess hair growth; age nine; inadequate treatment two years before.* A, *Note excess hair on legs, forearms, about face.* B, *eight months later. Although not too well shown because of motion, excess hair has fallen out; initial blood cholesterol* 394 *mg. per* 100 *cc.; urinary* 17-*ketosteroids* 1.34 *mg. per twenty-four hours.*

to thyroid and evidence of clinical improvement. For example, in Case 5 the metabolic rate was kept at a moderately high level, which could be considered hyperthyroid, and yet clinically, except for a pulse average of 90–100, the patient showed little evidence of excessive thyroid dosage. The dose was 2 gr. per day.

A return to normal growth rate should be the primary objective. Blood cholesterol determinations are useful in correlation of the effects of treatment in that an attempt should be made to keep the level below 180 mg. per 100 cc. or lower in the younger age group. We have rarely believed it necessary to give more than 2 gr. of thyroid per day. It is well not to lose sight of the normal higher pulse rate in children in determining dosage. Of more importance in regulating dosage is the child's general behavior, i.e., undue irritability and nervousness, indicating excess thyroid dosage.

What are the indications for removal of goiter? The possibility of malignant degen-

TABLE II

CRETINISM WITHOUT GOITER

Case and Sex	Age of Onset	On Admission			Mental Status*	Adequate Previous Treatment	Remarks	Results	Growth Curve on Fig. 13
		Age, Years	Height Age, Years	Bone Age, Years					
1 F	5 yrs.	15	12		Retarded	No	B.M.R. −44%.	Good physical development	Yes
2 M	Infancy	4	2⅔	½	Normal	No	Unable to sit up at 18 mos., walked first at 3 yrs.	Excellent to date	Yes
3 F	Infancy	4½	N.R.†		Retarded	No	Failure to grow, pot-belly, stubby hands, dry skin, constipated.	Doing well on 1 grain of thyroid daily	No
4 F	Infancy	8	7	3½	Normal	No	Menarche at 14; walked at 18 mos., talked at 3½ yrs.; 1st tooth at 1 yr.	Excellent	Yes
5 F	Infancy	18	8	11¼	Retarded	No	First B.M.R. −18%; kept between +20% and +35%; high grade deficiency, treated off and on; pot-belly, dry skin, classical facies.	Doing well on 2 grains of thyroid daily	Yes
6 F	Infancy (3 mos.)	26	N.R.		Retarded	Yes	Late result of infantile myxedema; B.M.R. −19%; pt. not seen again until age 43 (1945); ht. 64½ in. On thyroid, 2 grains daily.	Good result on thyroid since 3 mos. of age; low grade intelligence	No
7 F	Infancy	14	9	7	Retarded	No	One of twins; other normal; typical facies, dry skin, sluggish mentally.	Good	Yes
8 F	3 yrs.	16	9½	9	Retarded	No	Sluggish, dry skin, slowing of growth.	Good physical development	Yes
9 F	Infancy	7	3½	¾	Normal	No	Unable to walk until 18 mos. and not alone until 7 yrs.; mentally sluggish; fat.	Excellent	Yes
10 F	5 yrs.	18	10		Retarded	No	On admission, ht. 54 in., wt. 140 pounds; B.M.R. −19%; blood cholesterol 334 mg. %; started on 2 grains of thyroid.	No follow-up in 6 mos.	No
11 F	10 yrs.	14	10	8½	Normal	No	B.M.R. −21%; onset around 10 yrs. of age; not retarded mentally although somewhat sluggish; dry skin, hair.	Excellent	Yes
12 F	11 yrs.	33	14		Normal	No	Treated 1 yr. only, 11 yrs. previously; ht. 61¾ in.; blood cholesterol 420 mg. % on admission; put on 1 grain of thyroid daily.	Not seen after 1 yr.	No

TABLE II (*Continued*)

Case and Sex	Age of Onset	On Admission			Mental Status*	Adequate Previous Treatment	Remarks	Results	Growth Curve on Fig. 13
		Age, Years	Height Age, Years	Bone Age, Years					
13 M	Before 9 yrs.	12	6½		Retarded	No	Physical development on adequate dosage, 2–3 grains thyroid daily; not seen in thyroid deficient state because of taking thyroid.	Good	Yes
14 F	Before 2 yrs.	9	5½	7	Retarded	No	5 yr. old appearance; ht. 42¼ in., wt. 59¾ pounds; hair fine, silky, body hair heavy especially arms, legs, back. Eyebrows thick, skin coarse, rough. Blood cholesterol 394 mg. %. Androgens 1.34 mg. per 24 hrs.	Growth rate normal in 6 mos.; most superfluous hair fell out.	No
15 M	3 mos.	12	9	5¼	Retarded	No	Admission ht. 50¼ in., 69 pounds. Blood cholesterol 202 mg. % on ½ grain thyroid when taken. Grew 1½ in. in 7 mos. on 1½ grains a day.	Good	No
16 F	2 yrs.	7	5¾	5¾	Normal	No	Stopped growing at age 2, resumed growth with thyroid for 2½ yrs., then medication discontinued. On admission ht. 43 3/16 in.; 53 pounds. Blood cholesterol 263 mg. %. Excessive hair growth for age.	Early treatment prevented retarded mental age	No
17 F	2–3 yrs.	13	8½	11	Normal	Yes	Admission ht. 50 in., wt. 70 pounds; blood cholesterol 172 mg. %. Taking thyroid. Normal growth rate maintained with thyroid.	Early treatment prevented retarded mental age	No
18 F	Birth	21	13½	Mature	Retarded	Yes	On thyroid since 3 mos. old. Now taking 3¼ grains daily; ht. 60¾ in. Blood cholesterol 119 mg. %. Also has asthma.	Mentally retarded	No

* Mental status refers to mentality on treatment but not to the sluggish mental condition before treatment was instituted.

† N.R. = Not recorded.

TABLE III

CRETINISM WITH GOITER (OR PALPABLE THYROID)

Case and Sex	Age at Onset	On Admission			Mental Status	Adequate Previous Treatment	B.M.R., Per Cent	Date of Operation	Type of Goiter and Pathologic Report	Remarks	Results	Growth Curve on Fig. 13
		Age, Years	Height Age, Years	Bone Age, Years								
A. "Endemic Type" Goiter in Infancy and Childhood with Concurrent Thyroid Deficiency												
19 M	Birth	1¾	1	1½	Poor	No				Dysphagia at 3–4 mos. due to enlarged tongue. Gastrostomy done elsewhere. Poor parental cooperation. Thyroid tissue culture implantation without result.	Aside from mental status, improved on small doses of thyroid but greater improvement on adequate dosage. End result poor.	Yes
20 F	5 yrs.	11	8½	7¼	Normal	No	−32			Duration 6 yrs. Admission ht. 50 in., wt. 62½ pounds. Blood cholesterol 376 mg. %. On thyroid 1½ grains daily.	Doing well. Grew 2½ in. first 9 mos. of therapy.	No
21 M	Birth	8	11 (at 15)		Retarded	No	−5	1927	Fetal adenoma	Reduction of size of recurrent goiter on adequate thyroid dosage; on 1/80 grain thyroxin daily.	Good result. Has become watchmaker.	Yes
22 M	Infancy	11	8	4½	Retarded	No		1939	Fetal adenoma	On 1½ grains of thyroid; speech defect not improved	Good result. Stuttering improved.	Yes
23 M	4–5 yrs.	14	7	4	Retarded	No	−36		Substernal goiter	3 children in family with goiter. Descent of testes with treatment. See sister, Case 28.	Good physical progress when last seen.	Yes
24 F	7 yrs.	16	14¼ (at 17)		Retarded		−10	1933	Colloid adenoma with hyperplasia	Blood cholesterol 398 mg.%. Final ht. 62½ in. On 2 grains of thyroid daily.	Poor	No
25 F	9 yrs.	23	12	Adult	Slow	No	−28	1931 (elsewhere)	Recurrent nodular goiter with myxedema	Disappearance of goiter with 2 grains of thyroid. Blood cholesterol 194 mg. %. Ht. 61½ in.	Excellent	No
26 F	10 yrs.	22	12 (at 20)	Adult	Retarded	No	−16			Irregular treatment; none for 7 mos. Enlargement of thyroid since then; classical myxedema. Blood cholesterol 476 mg. %. Marked reduction in size. On 2 grains thyroid. Final ht. 61 in. Albuminuria decreased on thyroid. Moderate hypertension.	Fair	No

TABLE III (*Continued*)

Case and Sex	Age at Onset	On Admission: Age, Years	On Admission: Height Age, Years	On Admission: Bone Age, Years	Age at Change of Thyroid Function	Mental Status	B.M.R., Per Cent	Date of Operation	Type of Goiter and Pathologic Report	Remarks	Results	Growth Curve on Fig. 13
B. "Endemic Type" or Congenital Goiter with Previous Thyroid Deficiency but Not Concurrent when First Seen												
27 F	2 yrs.	14	11¼	11	11–12	Alert, but mental age retarded	±0 −10	1936	Colloid adenoma with hyperplasia	Thyroid deficient until 11 when goiter and function increased. Ht. 56¼ in.; blood cholesterol 160 mg. %; wt. 69. Delayed puberty, no pubic hair. Final ht. after 4 yrs., 61 in.	Excellent progress on 1½ grains of thyroid. Normal physical development	No
28 F	Infancy	20	10¾	18–20	Before puberty age 17	Retarded ++	+12	1944	Colloid fetal embryonal adenoma	Ht. 55 in. at 20; stigmas of previous cretinism remained, thyroid function normal when seen. Blood cholesterol 176 mg. %, given thyroid with slight reduction of goiter, 16¾ to 15½ in.	Good	No
29 M	8 yrs.	38	11½	..	? date	Retarded +++	+6	1944	Colloid adenomas with hyperplasia	Typical cretin with normal thyroid function when operated on, postop. deficiency. Blood cholesterol 325 mg. %, ht. 56 in. One brother with large goiter operated on but otherwise normal (Case 34).	No change. Will not take thyroid	No
30 F	7 yrs.	10	6¾	6	? date	Retarded	+7	1932 (10 yrs.)	Colloid adenomas with hyperplasia	Developed thyroid deficiency. Cholesterol 300 mg. %, given thyroid. Follow-up ended in 1936. Ht. at 10, 46½ in.; at 14, 50¼ in.	Poor	No
C. "Endemic Type" or Congenital Goiter with Hyperthyroidism and Previous Thyroid Deficiency												
31 M	Birth	11 at 1st admission; 21 at 2d admission	6¾	5 Adult	10 16–17	Retarded	+12 +21	1931 1942	1st op. colloid adenoma; 2d op. colloid adenomas with hyperplasia	When first seen had no concurrent deficiency; gland increased in size 1 yr. previously. Operation. Put on thyroid 1 grain, which was not continued and when seen again was thyrotoxic, lost wt., excess sweating, palpitations, apparent spurt in growth after 17 yrs. of age. Reoperated.	Excellent	Yes

TABLE III (*Continued*)

Case and Sex	Age at Onset	On Admission: Age, Years	On Admission: Height Age, Years	On Admission: Bone Age, Years	Age at Change of Thyroid Function	Mental Status	B.M.R., Per Cent	Date of Operation	Type of Goiter and Pathologic Report	Remarks	Results	Growth Curve on Fig. 13
C. "Endemic Type" or Congenital Goiter with Hyperthyroidism and Previous Thyroid Deficiency												
32 F	Birth	14	9½	12	6–8	Retarded	+34	1944	Colloid adenomas	Typical cretin developing hyperthyroidism, given thiouracil and iodine before op. Developed postop. myxedema. Taking thyroid.	Good	Yes
33 M	Birth	18	12	13	13	Retarded	±0	1945	Colloid adenomas (degenerated)	Grew rapidly last 2 yrs. Ht. 57¼ in., clinically toxic in spite of B.M.R. ±0. Blood cholesterol 156 mg. %, pulse rate 88; wt. loss, tremor, excess sweating. See data on brother, Case 35.	Good	No

Case and Sex	Age at Onset	On Admission: Age, Years	On Admission: Height Age, Years	On Admission: Bone Age, Years	Mental Status	B.M.R., Per Cent	Date of Operation	Type of Goiter and Pathologic Report	Remarks	Results	Growth Curve on Fig. 13
D. "Endemic Type" or Congenital Goiter with Adequate Thyroid Function and No Stigmas of Previous Deficiency											
34 M	9 yrs.	29	..	..	Normal	+1	1937	Colloid adenoma	May have been slightly toxic. Pulse 80. Appeared normally developed. Brother of Case 29.	Excellent	No
35 M	Birth	20	17	..	Normal	+4	1944	Colloid adenoma	Ht. 69 in., B.M.R. postoperatively −33%. Given thyroid. Brother of Case 33.	Good	No

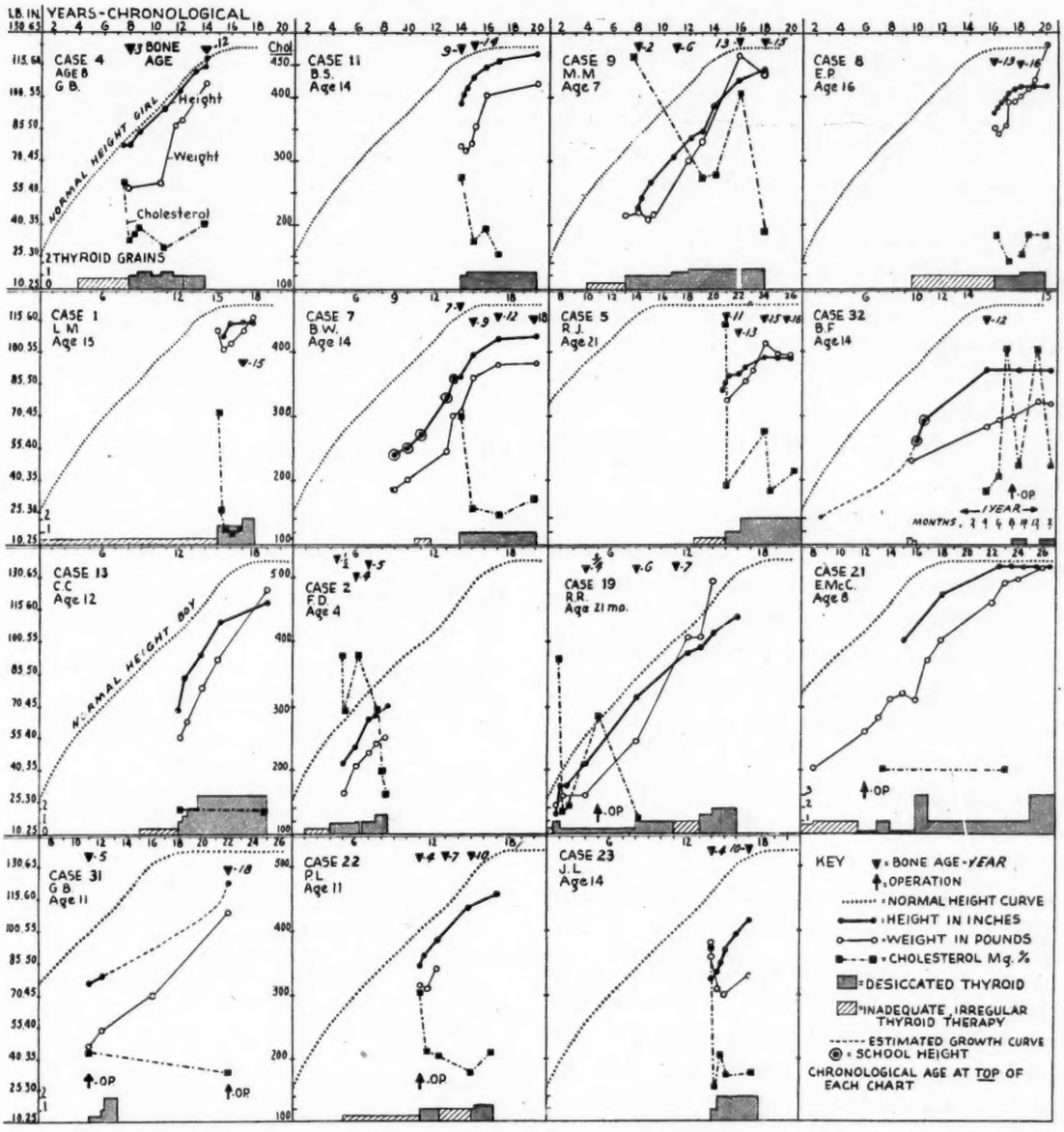


FIG. 13. *Growth chart of fifteen patients followed and treated for periods of from three years to maturity. Cases* 1 *through* 18 *are cretins without goiter* (*Table* II)*; Cases* 19, 21, 22 *and* 23 *are cretins with goiter and concurrent thyroid deficiency when treatment was started* (*Table* IIIA)*; Cases* 31 *and* 32 *represent cretins with hyperthyroidism* (*Table* IIIC)*. To be noted especially is the sensitivity of blood cholesterol to thyroid medication in cretinism; the resumption of normal rate of growth, and the subnormal final heights reached.*

eration within a discrete fetal adenoma must be considered, and is considered an indication for removal. If the child is definitely thyroid deficient, desiccated thyroid should be administered in the hope of reducing the size of the goiter. If this is unsuccessful and the goiter is large and unsightly, it should be removed for cosmetic purposes, even though desiccated thyroid may have to be taken continuously. In instances in which thyroid function has returned to normal, indications for removal are the same as above, for the goiter in this type is not likely to change in size on giving thyroid. In the cretin who has developed hyperthyroidism, subtotal thyroidectomy is indicated. Following operation, the child's course should be watched, and thyroid administered to lessen

the possibility of recurrence of goiter, to prevent the onset of probable myxedema and to attempt to maintain a normal growth rate.

SUMMARY AND CONCLUSIONS

1. A review of the different types of cretinism has been presented.

2. The etiology of cretinism has been discussed in light of recent advances in the knowledge of thyroid physiology.

3. A series of thirty-five cases of cretinism is reviewed, twins being involved in one instance.

4. It has been demonstrated that cretins with goiter may retain their thyroid deficiency, develop normal thyroid activity or even develop hyperthyroidism.

5. Spontaneous return to normal thyroid function or treatment with desiccated thyroid will advance bone age to, or beyond, height age and bring about a normal rate of growth, but the relationship between height age, mental age and chronological age is not altered.

6. The clinical and diagnostic features of cretinism are presented.

7. While mental age attained was near normal in only three cases, treatment has been considered worth while since the majority who have matured are able to earn their own living.

8. Early recognition and adequate treatment are paramount.

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Seminar on Antibiotics

The Treatment of Subacute Bacterial Endocarditis with Antibiotics*

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DURING the past three years a revolutionary change has taken place in the treatment of bacterial endocarditis. This by no means rare infection had previously carried a staggering mortality; in fact, before the advent of sulfonamides, recovery was almost unheard of.[1,2] Even with these relatively promising antibacterial agents, results were still poor. At best, 10 per cent recoveries were reported with sulfonamides alone, although in some small series,[3] 25 per cent cures occurred when fever therapy was employed in addition. The appearance of penicillin upon the scene has altered the picture dramatically, although early experiences with this agent were somewhat discouraging. Dawson and Hobby[4] reported the recovery of two patients treated in 1942 and 1943; but since other investigators, using doses now known to have been inadequate, failed to eradicate the infection in a number of patients, the drug was not released for the treatment of this disease until after Loewe et al.[5] reported successful treatment of seven patients with larger doses of penicillin in combination with heparin. During the past two years numerous papers [6–16] have appeared from clinics throughout the country reporting varying degrees of success and employing widely differing courses of therapy. One fact now clearly apparent is that penicillin cures an unprecedented number of patients with this disease. Several hundred patients have now been followed for many months after therapy and, in the group treated under the Committee on Chemotherapeutic and Other Agents of the National Research Council, the percentage of cures is approximately 60 per cent.[16] The author has personally followed a series of fifty patients treated at the Presbyterian Hospital and the opinions herein expressed are based largely on this experience. It seems unnecessary to present at this time much of the pathology, pathogenesis and historical material concerning bacterial endocarditis. Rather it is our purpose to attempt an evaluation of the chief problems involved in the diagnosis of the disease and the management of these patients.

DIAGNOSIS

Before the modern chemotherapeutic era, there was no urgency about making an early diagnosis of subacute bacterial endocarditis. The patients all died in any event, and the tendency naturally prevalent was to wait for the full-blown clinical picture before committing oneself. With the recent change in the therapeutic outlook such an attitude is no longer justifiable. It now becomes highly important to establish the diagnosis and to get treatment under way at the earliest possible time. This is difficult with a disease as protean in its symptoma-

* From the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York. The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

tology as bacterial endocarditis, especially as the onset is notoriously insidious. If early diagnosis is to be made, physicians must consider the possibility of bacterial endocarditis in any patient with valvular heart disease who has fever for more than a week. Furthermore, it must be appreciated that any of the classic stigmas of the disease may be absent in a given case. We have seen occasional cases in which no significant heart murmur was present after several weeks of illness although this is distinctly uncommon. Fever also may be lacking for long periods of time and, of course, not uncommonly embolic phenomena, splenomegaly and anemia are completely absent. The ultimate criterion for establishing the diagnosis obviously must be repeatedly positive blood cultures. The occurrence of transitory bacteremias without bacterial vegetations should be kept in mind, and basing a diagnosis on one or two positive cultures may be open to question. Certain other diseases frequently may be confused clinically with subacute bacterial endocarditis, i.e., rheumatic heart disease with auricular fibrillation and auricular thrombi giving rise to embolization. Recrudescences of rheumatic activity, and, in fact, any febrile disease in subjects with rheumatic heart disease must be differentiated. Disseminated lupus erythematosus can at times simulate bacterial endocarditis so closely as to be an extremely difficult problem in diagnosis. It is probably true that many cases described as subacute bacterial endocarditis in a bacteria-free stage have actually been instances of lupus. There is no doubt, however, that in a small proportion of cases, perhaps 10 per cent, positive blood cultures are obtained only with great difficulty if at all. In such instances, after all attempts to recover the organism have failed it is justifiable to treat the patient with penicillin anyway, but under these circumstances one is in the dark as to what dosage to employ and as to the results to be expected. Furthermore in such cases the infecting agent not infrequently turns out to be one of the less common organisms which may require some agent other than penicillin or unusually large doses of the latter for its inhibition. Therefore, it is strongly urged that unless the clinical condition of the patient is so serious as to demand immediate therapy, treatment be postponed until several unequivocally positive cultures are obtained and the organism's sensitivity to available chemotherapeutic agents determined.

BACTERIOLOGY

Organisms Encountered. At one time or another almost every known variety of bacterium has been reported as causing subacute bacterial endocarditis, but it is generally accepted that in approximately 95 per cent of cases the infecting agent is a streptococcus of the viridans or non-hemolytic type. The classification of this group[19] is not entirely satisfactory at the present time and no serological or other differentiation of the pathogenic and non-pathogenic strains exists. In general, Brown's classification, based on hemolysis of blood agar and dividing streptococci in general into alpha, beta and gamma hemolytic forms, is most frequently used.

The beta hemolytic streptococci are those that cause a true hemolysis of red blood cells. This group has been subdivided by Lancefield into a number of serological groups based on antigenic fractions within the bacterial cell.

The gamma hemolytic streptococci are those that cause no change in the appearance of the red blood cells. They are often referred to as non-hemolytic, anhemolytic or indifferent streptococci.

The alpha hemolytic streptococci are those that cause a green discoloration of the red blood cells in the medium and are

generally classified as Streptococcus viridans. These are also spoken of as non-hemolytic or green streptococci.

The alpha and gamma hemolytic streptococci are those most commonly associated with subacute bacterial endocarditis. These two groups are not entirely distinct. Strains of Streptococcus viridans often fail to produce greening in young cultures or when grown in certain species of blood. Under such conditions they may appear anhemolytic. Variation between these two forms has been observed by many investigators. Although the majority of non-hemolytic strains do not fall into any of the Lancefield serological groups, a few strains including both alpha and gamma types, can be classified in this manner. Predominant among those that often fit into the serological classification are the enterococci (Streptococcus fecalis). The enterococci are distinguished by their heat resistance, their ability to grow in 6 per cent sodium chloride solution, and by a high degree of resistance to penicillin.

Various investigators have subdivided the non-hemolytic streptococci into a variety of types, Streptococcus salivarius, bovis, mitis, etc., by means of fermentation reactions. There has been no advantage in differentiating organisms from subacute bacterial endocarditis into these types as no specific one can be correlated with this type of infection and no correlation with susceptibility to penicillin has yet been demonstrated.

Loewe et al.[20] distinguish an organism which they call Streptococcus s.b.e. isolated from cases of this disease which were apparently unusually refractory to treatment. No data are presented on the *in vitro* penicillin sensitivity of this organism and at present the importance of their observations cannot be judged until further information becomes available.

In brief, the one important characteristic of a strain, from a practical point of view, is its susceptibility to the action of penicillin. Unfortunately, this varies from strain to strain in an unpredictable manner and over a very wide range. By the *in vitro* tests, anywhere from .01 to 10 units or more per cc. may be the inhibiting level.[21] It therefore is apparent that if treatment is to be rational, *the in vitro sensitivity of the individual strain must be determined in every case.* Fortunately, about 90 per cent of the streptococci isolated from patients with subacute bacterial endocarditis are inhibited *in vitro* by .1 unit or less per cc.[16]

Blood Cultures. If there is difficulty in obtaining positive cultures in clinically evident cases of subacute bacterial endocarditis, several possible sources of error should be considered and one must be on the lookout for unusual organisms. The media used must be checked to be sure that the pH is satisfactory and the broth properly nutritious. At times growth can be obtained under carbon dioxide or in anaerobic cultures when ordinary methods fail. Pour plates should be made as they often facilitate the interpretation of doubtful broth cultures. The inoculum of blood must be adequate; in our hands 5 cc. to about 60 to 100 cc. of broth, and 1 and 2 cc. of blood to 10 cc. of agar in pour plates have proven satisfactory. Many investigators have advocated taking arterial blood cultures, but Beeson et al.[17] have shown that colony counts from arterial blood are not significantly higher than those from venous blood drawn from the antecubital vein. In our experience nothing is to be gained by this procedure.

All blood cultures should be incubated for at least two and preferably three weeks before they are declared negative. At times slow growing organisms are missed through premature discarding of cultures. Slow growth is especially common in blood cultures from patients in an early relapse

after treatment with penicillin. Furthermore, the organisms when first isolated under these conditions may be very pleomorphic and unless observed carefully in subculture could easily be mistaken for contaminants.

DEVELOPMENT OF PENICILLIN RESISTANCE

In the event of a relapse of the infection after penicillin therapy, the newly isolated organism should be investigated again as to penicillin sensitivity. It is a well known fact that certain organisms when exposed to a sublethal concentration of an antibacterial agent emerge as resistant to the agent in question. Whether this represents a biochemical adaptation on the part of the bacterial cell or only a selection of already resistant individuals has not been entirely settled. The evidence on the whole favors the latter interpretation, however. At any rate, this phenomenon very rarely takes place with the non-hemolytic streptococci. We have encountered only one clearcut example in a series of fifty patients, many of whom relapsed after inadequate therapy, and some repeatedly over periods as long as six months without showing any change whatever in the penicillin susceptibility of the infecting organisms.

PENICILLIN MEASUREMENTS

All determinations of penicillin concentrations in body fluids and of susceptibility of organisms to penicillin *in vitro* are biological measurements based on inhibition of bacterial growth under certain standardized conditions. The inherent errors in the methods used are large and comparison of results in different laboratories where various technics are employed discloses large discrepancies. In addition to differences in methods and technics, which may explain some of the discrepancies, there is still another factor of possible importance. It must be remembered that there are at least four different penicillins called F, G, X and K, which are not only chemically distinct but have somewhat different activities against various organisms. The significance of these various forms in relation to penicillin measurements in body fluids remains to be seen, but almost all reported measurements of penicillin concentrations and activity to date have been made in ignorance of the relative amounts of these four fractions in the material being tested. It is not difficult, therefore, to see why discrepancies exist even in the same laboratory from time to time.

In spite of the above mentioned sources of error, and probably many others as well, measurements of penicillin blood levels and of the *in vitro* sensitivity of infecting organisms have provided much information which has proven very helpful in guiding therapeutic management of clinical infections. The correlation between *in vitro* measurements and clinical results has, in fact, been surprisingly good. In general, organisms inhibited *in vitro* by less than .1 unit of penicillin per cc. have been considered sensitive, and in a high proportion of patients harboring them, therapy has been successful. Organisms requiring from .1 to .5 unit per cc. have been considered moderately resistant, and clinical results have shown that larger doses are needed to eradicate these infections. In cases with from .5 to 10 units per cc. *in vitro* sensitivities, very large doses of penicillin have been resorted to in many instances without obtaining cures. So far there have been no reports of success in the treatment of patients whose organisms require 10 units per cc. or more on any dose of penicillin.

By the methods used in this laboratory penicillin serum levels have shown wide variations from patient to patient, and from time to time in the same patient, on the same dosage by constant drip. As shown in Table 1, the level obtained on various doses

can be predicted only very roughly in a given case. The averages, however, give one some idea of what to expect. It has been our policy to maintain serum levels at least four times the amount required for *in vitro* inhibition of the patient's organism, and in certain instances an even greater excess has been found necessary.

TABLE I
CORRELATION OF PENICILLIN SERUM LEVELS WITH TWENTY-FOUR-HOUR DOSE ADMINISTERED BY CONSTANT INTRAMUSCULAR OR INTRAVENOUS DRIP

Daily Dose (Units)	Aver. Serum Level (u/cc. of Serum)	Range of Values (u/cc. of Serum)	No. of Determinations
200,000	.07	.03 to .28	19
300,000	.09	.07 to .28	4
500,000	.2	.025 to .8	113
1,000,000	.56	.5 to 6.4	42
2,000,000	1.6 to 2.24	.56 to 4.48	21
5,000,000	3.2	1.6 to 12.8	16
10,000,000	6.66	6.4 to 51.2*	17
20,000,000	25.0	3.2 to 51.2	4

Serum levels were determined according to the method described elsewhere.[18]

*This very high level occurred in a patient with transient azotemia.

THERAPY

General Considerations. There is agreement among most observers now that penicillin in adequate dosage for a long enough time is the important factor in the cures obtained in subacute bacterial endocarditis. The use of anticoagulants such as heparin or dicumarol has been largely abandoned since it has become clear that results with penicillin alone are as good or better than those obtained by combined penicillin and anticoagulant therapy. The author has had experience with both forms of treatment and believes there is little doubt as to the validity of this conclusion. Heparinization simply adds the danger of hemorrhage, increases the discomfort of the patient and complicates management without contributing favorably to the outcome.

Likewise there has been no evidence to date that the use of sulfonamides in conjunction with penicillin is of any value, although final judgment on this point cannot yet be passed.

The main differences of opinion are concerned with (1) route of administration, (2) optimum daily doses, (3) duration of therapy, and (4) criteria for judging progress of the patient under treatment. These points will be considered below although sufficient data have not as yet been accumulated to permit of definitive recommendations in all of them.

Whatever methods of giving penicillin or other antibacterial agents one adopts, a relentless persistence in the treatment of this infection is essential. One is not justified in abandoning hope of cure until cardiac failure or other complications of the disease make the outlook clearly hopeless. A number of patients have eventually been cured after five or six relapses and have returned to active useful lives. The recuperative capacity of many young patients who have appeared to be virtually moribund with this disease has been quite astounding.

Route of Administration. Satisfactory results have been reported in the treatment of subacute bacterial endocarditis with penicillin by all parenteral routes. So far the oral administration of the drug has not produced consistently high enough blood levels to warrant the use of this method in treatment of such a serious and relatively resistant infection as bacterial endocarditis. Some investigators[7,9,12] believe that in this disease a constant drip, either intravenous or intramuscular, should be used routinely, the arguments in favor of continuous administration being that inhibiting blood levels can be maintained fairly uniformly day and night, and that some patients have apparently done well on the constant drip after failure on fractional intramuscular administration. On the other hand many patients

have been cured of the disease on intramuscular penicillin given every two or three hours, and there is no clearcut evidence that maintenance of constant high blood levels is essential. In fact, Gerber[15] advocates intermittent administration with booster doses as superior to continuous drip, arguing that it is better to attain really high blood levels at intervals than to maintain moderate but constant levels. At present this issue cannot be settled definitely; but it seems reasonable to treat patients by the simpler method first, at least in those cases in which the organism is not unduly resistant to penicillin *in vitro*, and to resort to the more laborious constant drip methods only when a course by fractional intramuscular injection has failed.

Daily Dosage. It is difficult to know what recommendations to make as to the problem of penicillin dosage in this disease. Only broad generalizations can be made as to policy and each case must be individualized on its own merits. There is no doubt that many failures in the treatment of subacute bacterial endocarditis have been due to inadequate dosage of penicillin; and now that the drug is available in large quantities, one is justified in adopting a policy of trying to err on the side of giving an excess, especially as the drug is essentially harmless and the disease so serious. The Committee on Chemotherapeutic and Other Agents of the National Research Council has recommended a daily dose of from 200,000 to 300,000 units for the average case. On this dosage, however, there have admittedly been a number of failures and it seems safer to employ larger doses in the hope of cutting down still further the number of relapses. In patients whose infecting organism is sensitive to 0.1 unit of penicillin per cc., it is suggested that at least 500,000 units a day be administered. If the organism is more resistant to penicillin *in vitro* still larger amounts should be given, aiming to attain average blood levels at least four or five times the amount necessary for *in vitro* inhibition of growth.

Duration of Therapy. The problem of duration of treatment is intimately tied up with the question of daily dosage. Investigators have on the whole fallen into two camps, on the one hand those favoring small doses over prolonged periods of time and on the other hand those favoring more intensive treatment for shorter periods. All are agreed that two weeks of therapy is the shortest period which can be recommended. Apparently cure may be brought about in two ways; either by direct killing of all organisms in the vegetation through penetration of high concentrations of penicillin, or by surface sterilization and ultimate control of deep infection through the normal defense mechanisms of scarring, endothelializing and healing over a longer period of time. In a disease in which lost time means progressive and irreversible valve damage it seems wise to attempt the earliest possible eradication of infection. If inadequate doses are given over a period of several months, blood cultures may be sterile all during therapy; but serious valvular damage may be occurring in the meantime with prompt recurrence of positive cultures at the end of treatment. We, therefore, recommend in general trying first an intensive course of three or four weeks' duration; then if relapse takes place one must give larger doses and possibly continue for a longer time.

CLINICAL COURSE OF PATIENTS UNDER THERAPY

Unfortunately, there is no satisfactory criterion for cure while therapy is in progress. Wide variations in clinical response have been observed. Some patients improve promptly in all respects with rapid subsidence of all clinical and laboratory evidences of persisting infection and yet relapse

when treatment is stopped. Others appear to be critically ill with persistent fever, anemia, embolic phenomena and all the signs of active infection except that the blood cultures are negative, and yet when the therapy is discontinued they gradually improve and eventually turn out to be cured. There is no questioning the fact that fever, elevation of the sedimentation rate and embolization may persist for several weeks after a successful course of therapy with eradication of all infection. Of course, continued positive blood cultures for more than a few days after starting treatment are unequivocal evidence of inadequate dosage and call for a prompt change in the therapeutic program. On the other hand, there is no way of being sure that the infection has been permanently controlled short of following the blood culture after stopping treatment. Fortunately, relapses when they occur usually become evident by recurrence of positive blood cultures within two weeks of cessation of therapy, though not infrequently clinical signs of relapse may not appear for several weeks after reappearance of organisms in the blood. No late relapses have occurred in our series and reports of such in the literature are very infrequent. Hence it is possible within a few weeks after stopping treatment to tell with a high degree of probability whether or not it has been successful.

TREATMENT OF RESISTANT CASES

Although the correlation between *in vitro* sensitivity of the infecting organism to penicillin and the results of treatment is quite good, it is by no means perfect. Some patients whose streptococci are quite sensitive relapse after one or more of the usual courses of therapy for no obvious reason. Factors such as duration of the disease, valves involved, and clinical severity of the infection as such have not appeared to have any bearing on this problem. We have observed, however, that in most resistant cases there have been few or no embolic phenomena. Presumably one reason for the refractoriness of these cases is that the vegetations are large and dense, requiring greater concentrations of penicillin for penetration to their depths. Also there is reason to believe that when there is calcification of the involved valves, unusually large doses may be required. In such refractory cases or in those harboring resistant organisms good results have been obtained in a few cases on truly heroic doses of penicillin.* One patient, a man of sixty-five with arteriosclerotic disease and calcification of the aortic valve was treated with 400,000 units daily by fractional intramuscular injection for six weeks and with 500,000 units a day by constant intramuscular drip for three weeks but relapsed shortly after each course. He was then given 1,500,000 units daily by constant drip for two weeks but again relapsed. His organism, a Streptococcus viridans, which had originally been inhibited by .03 unit of penicillin now required .5 to .8 unit for inhibition by the *in vitro* test and remained unchanged thereafter. Subsequent courses on various doses including 2,000,000 units a day for three months by intramuscular injection as well as 5 and 10 million units for twelve days by constant intravenous drip all failed to eradicate the infection. Blood cultures remained sterile during therapy and for about two weeks after, but subsequently again became positive. The final course of treatment, consisting of 20,000,000 units a day for sixteen days, was followed by consistently negative blood cultures and absence of any signs of persisting infection. The patient unfortunately died one month later of cardiac failure and at autopsy was found to have a heavily calcified and severely eroded aortic valve. There were no fresh vegetations and

* The penicillin for these studies was very kindly supplied by Mr. John L. Smith, President of Chas. Pfizer & Company, Brooklyn, N. Y.

cultures of both heart's blood and ground-up valve grew no streptococci.

This case proved extremely refractory to treatment out of proportion to the penicillin resistance which appeared in the infecting strain. One can speculate that the reason for this lay at least partly in the nature of the vegetations and in the walling off of infection in calcified masses. The situation might be compared to the treatment of an osteomyelitis of the aortic valve. The important point is that in spite of these circumstances sterilization of the lesions eventually was achieved, though too late to save the patient. What might have happened if massive doses had been given earlier is a matter for conjecture. Our experience with patients such as this one has convinced us of the need for further investigation of the therapeutic possibilities of maximal penicillin dosage.

Two other patients, infected with organisms requiring 1 unit of penicillin per cc. for inhibition, apparently have recently been cured. One received 5,000,000 units a day by constant drip for three weeks, the other 10,000,000 units daily for a similar period.

A successful outcome appears to have resulted from combined penicillin and streptomycin therapy in another very refractory case. The infecting organism in this instance was an enterococcus requiring 8 units of penicillin per cc. for inhibition, and the patient had received up to 2,000,000 units daily at another hospital during many weeks of treatment without even transitory sterilization of the blood stream infection. Because the organism proved to be relatively resistant to streptomycin *in vitro* but was inhibited by penicillin and streptomycin together in attainable concentrations, she was given 4,000,000 units of penicillin by constant drip together with 4 Gm. of streptomycin by fractional intramuscular injection daily for four weeks. The patient seems to be well now several months after therapy, but it is too early to pass final judgment on the result.

These patients are mentioned here briefly to show that some encouraging results are being obtained in very difficult cases. The possibilities with very large doses of penicillin and with various forms of combined antibacterial therapy have hardly begun to unfold but deserve active investigation. Certainly no cut and dried programs of therapy can be outlined at this time. One can only advise finding out everything possible about the organisms by *in vitro* sensitivity tests to all available antibacterial agents, selecting a program which seems logical on that basis and pursuing treatment with dogged determination. The disease is fundamentally amenable to a chemotherapeutic approach, we know, and various regimens must be tried until either cure results or the patient's condition becomes clearly beyond repair.

MANAGEMENT OF PATIENTS WITH A PATENT DUCTUS ARTERIOSUS

Even before penicillin was available a few patients with bacterial implantation on a patent ductus arteriosus were cured of the infection by ligation of the ductus. There were, however, many failures on surgical treatment alone. Our policy at the present time is to try to cure the infection with chemotherapy first. If this is successful, the patient is then studied several months later for the purpose of deciding whether or not ligation is advisable. If there is any doubt as to the presence of other congenital lesions such as pulmonic stenosis and ventricular septal defect, the right heart is catheterized in an attempt to settle the question; for if such a right to left shunt is present, ligation of the ductus may be harmful. When possible, we prefer postponing operation until there has been time for healing of the vegetations. The operation can then be done as an elective procedure with the patient in

the optimum condition. If chemotherapy fails after a reasonable trial, one has to resort to ligation and continued chemotherapy after operation in an all-out attempt to eradicate the infection.

PROPHYLAXIS

It is generally accepted that one of the common sources of the original bacteremia which starts up a bacterial endocarditis is tooth extraction. Presumably any operative procedure around infected tissue is hazardous in a patient with valvular heart disease, but dental operations occur most frequently. Urinary tract and rectal procedures also should be considered as possible sources of danger.

What constitutes an adequate prophylactic regimen at the time of such operations in patients with valvular heart disease has not been established. We have had one patient who developed a reinfection after extraction of a tooth in spite of full doses of sulfadiazine for forty-eight hours combined with penicillin, 25,000 units intramuscularly every three hours for the first twenty-four hours. On the basis of this experience we are now starting sulfadiazine six hours before operation and continuing full doses for several days. In addition, 100,000 units of penicillin are given immediately before and after operation, followed by 100,000 units every three hours for at least twenty-four or forty-eight hours. Whether or not this regimen will prove satisfactory remains to be seen, but in any event patients should all be clearly told that they must never submit to oral surgery except under circumstances in which prophylactic measures can be instituted.

RESULTS OF PENICILLIN THERAPY IN STREPTOCOCCAL SUBACUTE BACTERIAL ENDOCARDITIS

Of forty-nine patients with this disease treated at Presbyterian Hospital during the past four years, forty-one (83 per cent) are at present living and well with an average follow-up of eighteen months. Four of the eight deaths occurred from causes other than uncontrolled infection, and in three of these at autopsy no bacteria were found in the healed lesions. The infection has, therefore, been eradicated in 90 per cent of the cases treated. Three of the four patients in whom the infection was not controlled were treated before large amounts of penicillin were available. The fourth was a patient whose organism required 10 units of penicillin per cc. for inhibition, and in whom only transitory sterilization of the blood stream was achieved.

In summary, these results suggest that with persistent therapy, at times using as much as 20,000,000 units of penicillin a day, the infection is controllable in almost every case of streptococcal subacute bacterial endocarditis.

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Conferences on Therapy

Treatment of Barbiturate Poisoning*

THESE are stenographic reports, slightly edited, of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students, and visitors. The next report will appear in the September issue and will concern the Treatment of Coronary Disease.

DR. MCKEEN CATTELL: The statistics of the Medical Examiner's office in New York City show that next to carbon monoxide, the barbiturates are the most frequent sources of poisoning, both suicidal and accidental. We had a conference on the treatment of poisoning by the barbiturates about two years ago and we are to review this subject again this afternoon. There has been a great deal of interest in this matter because of the increasing frequency with which this type of poisoning is encountered. It is a difficult form of therapy, requiring a good deal of judgment. We hope we can crystallize some information on the subject of the best procedures. Dr. Gold will open the discussion.

DR. HARRY GOLD: From one point of view, patients with barbiturate poisoning fall into four groups, two of which recover and the remaining two do not. The first is the group of patients who recover without any treatment. All they require is general nursing. The second is the group of patients who die regardless of how intensive and expert the treatment is. They have simply taken so large a dose that no antidote or method of treatment can save them. The third group embraces those patients who recover only because of expert management; without the most effective measures most effectively applied they would succumb. The fourth embraces those patients who die because of the treatment.

I have been in contact with a fair number of cases of barbiturate poisoning either through inquiries for advice or direct participation in their management. This experience impresses me with the fact that there is great need for better understanding of the basic problems involved in the course of poisoning by this group of drugs as well as in the various aspects of its treatment.

I have here a few memoranda concerning such cases which I just took out of my folder. Here is the case of the wife of a physician who is supposed to have taken twenty-three tablets of nembutal at about 1:00 P.M. She was found in coma about an hour later. I first learned about this case seven hours later when the physician called me for advice concerning the treatment and for a source of supply of picrotoxin. The only information that he had about her status was that she was in coma, that the blood pressure was 110, respiration 26, and heart rate 90. He had been looking after her from the beginning, but he did not know the state of her reflexes at the present time nor did he know how matters stood at the beginning, information which could be used as a basis for a decision as to whether the course in these seven hours had been stationary, or progressing downward or upward. Such information would be of the utmost value in deciding the treatment. There was a period of seven hours of management which passed by without yielding the slightest bit of the information that should have been obtained.

* From the Departments of Pharmacology and Medicine, Cornell University Medical College and The New York Hospital, January 10, 1946, New York City.

Here is another case: A few months ago I received a telephone call concerning a patient who took 21 gr. of sodium alurate and 9 gr. of seconal. She went into deep coma and it was now twenty hours after the dose. She was alert and carrying on a conversation. The reason for the telephone call was that the patient looked somewhat flushed; and although all physical findings were normal, the physician was worried that the treatment might not have been adequate and that some additional measures should be taken to insure recovery.

Here is a memorandum about a three-year-old child who had taken 19 gr. of phenobarbital twenty-four hours previously. Although the stomach was washed within an hour after the dose, coma developed with respiratory depression. He was given a total of 9 mg. of picrotoxin by intravenous injection in two doses within a period of about forty-five minutes, equivalent to about 45 mg. for an adult. It caused a prompt convulsion. That apparently was not what they bargained for when they started to use picrotoxin, hence the long-distance telephone call.

These are a few fairly good samples of the type of problems that need to be explored and crystallized in relation to the treatment of barbiturate poisoning.

Before any treatment is applied in a case of barbiturate poisoning, satisfactory orientation is desirable regarding two questions: first, how deep is the poisoning and second, has the material been completely absorbed?

It is very helpful to know the amount of the drug the patient has taken, but that information is frequently quite inaccurate, although it is well to have in mind that adults are practically certain to recover without specific treatment from oral doses of the order of 1 or 2 Gm. of any of the commonly used barbiturates.

I should like to recommend that the first thing one should do is to list on a sheet of paper the common guides to the depth of barbiturate poisoning: state of consciousness, depth and rate of respiration, blood pressure, heart rate, skin (warm, cold, wet, or dry), cyanosis, pulmonary râles, response to painful stimuli, width of the pupils, and reflexes (pupillary reactions, knee jerks, swallowing reflexes). One should indicate in a column the presence or absence of these signs by a plus or a zero. Entries are then made on this form as time passes, at intervals of fifteen minutes or longer depending on how severe the poisoning seems to be. This provides a convenient record, easy to examine and interpret as a guide to the therapy. Very often one decides to do nothing in a case when first seen because the barbiturate poisoning seems so mild, but one reverses the decision after observation for a few hours because the knee jerk which was present has now disappeared, or the pupil which reacted to light has now ceased to do so, or the pupil which was first small has now become widely dilated, or the blood pressure which was at first 120/80 has now declined to 80/70. It is my experience that unless one makes a chart of this kind with these various specific points clearly listed, the chance is high that the record will be incomplete in some details essential for a decision regarding the treatment two or three hours later. I cannot emphasize too strongly the fact that the type of treatment is often determined not by the state of the patient when first seen, but by the course which the poisoning has taken, and that course is clearly revealed by a record such as I have outlined.

Has the drug been completely absorbed? That is the next question which should be decided. If you can be fairly certain of the answer to this question, the problem before you is much clearer. It is one thing to expect that there is a great deal of the drug in the gastrointestinal tract, and that you can expect deepening effects as the result of con-

tinued absorption. It is quite another matter if you can be fairly certain that absorption is already substantially complete, and that the intensity of poisoning before you at the time is as great as the patient is likely to show. There is also the question of washing the stomach. In a paper by Fantus on the treatment of barbiturate poisoning in the *J. A. M. A.* (August 17, 1940), evacuation of the stomach is the first step advised in the case of a patient admitted to the hospital in coma. What possible advantage could there be in washing the stomach in a case in which there is information that the poison was swallowed at least twenty hours previously? All one does in a case of that kind by washing the stomach is to expose the patient to the added danger of aspiration pneumonia. It is true that one does not always know how long a period has elapsed since the drug was taken, but we should make use of the information in those cases in which one does know the approximate interval, and avoid useless and dangerous steps.

In connection with absorption, it is well to have in mind the fact that the barbiturates are fairly rapidly absorbed. A massive dose of a barbiturate given on an empty stomach can kill a cat in as short a period as seven minutes. Of course, if the barbiturate is taken shortly after a meal, the absorption is much slower. There is also the fact that a massive dose of a barbiturate may cause such severe irritation of the stomach with reflex closure of the pylorus that absorption is delayed. Taking all of these factors into consideration, however, I believe it is proper to say that if several hours have elapsed since the drug was taken, one may safely assume that absorption is substantially complete and that little is to be gained by washing the stomach.

By the same token, it is safe to assume that if six or eight hours have elapsed since the poison was swallowed, progressive deepening of the narcosis as the result of continued absorption is also unlikely. Such a decision, if based upon reasonably accurate facts, better defines the problem of therapy in the case in question. For example, if you encounter a patient in coma as the result of a barbiturate but the condition is satisfactory in the sense that the pupils are small and react to light, the skin is warm, the respiration is fairly satisfactory, and the blood pressure is 110/70, and if this is the state at the end of six or eight hours or longer following the dose, and if there is no reason for suspecting interference with absorption, you would do well to withhold specific antidotes and apply only general nursing care, since such a patient is almost certain to recover. I encountered a patient in such a state a few months ago. The drug had been swallowed about twenty hours previously. Although the general state was as I just described, the physician tried to restore consciousness by means of picrotoxin and metrazol. As I walked into the room I saw this apparently comatose patient suddenly kick his legs up into the air. The patient was having picrotoxin fits. This is precisely the type of patient I referred to in the first group, namely, those who do very well when they are left alone, and whose lives are endangered by the use of analeptics.

There is another point requiring orientation before therapy. No single system can be depended upon to reveal the true intensity of the poisoning by the barbiturates. There are, of course, those patients in whom all systems seem profoundly depressed. There are others, however, in whom one system may show fairly deep poisoning while another, fairly light. For example, there are those in whom all of the common reflexes that can be tested, are found to be absent, absent corneal and pupillary reflex, absent knee jerks, absent swallowing reflex, etc., but the respiration is fairly normal

and the blood pressure is satisfactory. There are others in whom several of the reflexes are found intact but the respiration is so profoundly depressed that it seems unlikely they will go on very long without the secondary effects of anoxia. There are still others in whom the respiration and reflexes reveal generally light narcosis, but in whom the blood pressure is extremely depressed to a level of, say 80/70. Clearly, the drug depresses the respiratory center more in one case, and the vasomotor center more in another case, and so on. A thorough examination at the beginning will clearly reveal what system it is which requires specific attention in treatment.

The secondary effects of anoxia must not be confused with primary poisoning. Many patients with barbiturate poisoning, when first found, have been lying in a state of narcosis for several hours and there is a picture of advanced poisoning involving all the systems, which may be deceptive, because the deterioration is chiefly the secondary effect of anoxia rather than the primary effect of the drug itself. As they lie there, the tongue falls back against the palate or pharynx, mucus collects in the bronchi, and together these factors so impair the respiratory exchange that a degree of poisoning is in evidence which seems to place the patient on the brink of disaster. Some of these patients are relatively lightly narcotized, and the whole picture is rapidly reversed by measures which improve the respiratory exchange. Pull the tongue forward, put in an air-way, administer oxygen by nasal catheter and remove the mucus from the upper part of the respiratory tree. After this is done, the patient begins to improve and with such speed as to leave no doubt that the recovery bears no relationship to the elimination of the drug. It is well to bear the factor of anoxia in mind because such patients, being only lightly narcotized, are very susceptible to the analeptics. Because of their profound depression, one sometimes judges that large doses of metrazol or picrotoxin are necessary. One is then surprised to find that even a small dose produces a convulsion. We should not be surprised about this when we bear in mind the fact that the appearance of the patient poisoned with barbiturate is often only in part the result of the direct depression by the drug, and may in a large part be due to the secondary depression by the anoxia.

In practically all current accounts of the treatment of barbiturate poisoning, one finds the recommendation to use one or another of the analeptic drugs, metrazol, coramine or picrotoxin. I think this is a mistake for a very large proportion of patients in coma as the result of a barbiturate recover without an analeptic. Why not use them just the same and give the patient the added chance of recovering even if he would have recovered without it? The reason is that the analeptic is itself a source of danger when used in effective amounts. I am not at all sure but that many patients are deprived of their chances of recovering by the liberal use of these drugs. Judgment as to what patient needs them and what patient is likely to do well without them is, therefore, decisive.

Let us consider for a moment the patient with barbiturate poisoning in coma, who seems fairly well from general appearances; the color is good, the skin is warm, the blood pressure is satisfactory, the pupillary reflexes are present, but the respiration is so slow and shallow that one has to strain to see the patient breathe. Here the indication for immediate treatment is clear, namely, the use of a respiratory stimulant. Caffeine is the material of choice. It may be given in a dose of 0.5 Gm. of caffeine and sodium benzoate intramuscularly or intravenously. The dose may be repeated two or three times at intervals of thirty minutes or more quickly in the case of the intravenous route

in order to produce or to maintain an increase in the depth and speed of respiration. This may also be accomplished at times by inhalation of a mixture of oxygen and carbon dioxide. Caffeine has the advantage over some of the other analeptics for this specific purpose because it rarely produces secondary depression of respiration and there is little or no danger of overdosage producing convulsions.

In another case the picture of poisoning may be similar to the one I just mentioned, but the breathing seems satisfactory, while the blood pressure is down nearly to a shock level of 80/70. Here other types of stimulants are clearly indicated, namely, neosynephrine or paradrine. These may be given in doses of 10 or 20 mg. by intramuscular injection, and repeated as necessary at intervals of thirty minutes or longer. They frequently boost the blood pressure to more satisfactory levels and speed up the circulation. This may be all that is necessary in a case of this kind. By such measures a patient who is likely to get into serious difficulties by the secondary effects of vasomotor depression is lifted into a state in which recovery is insured. The point about such cases is that they are only lightly narcotized, only one system such as the vasomotor or the respiratory centers being unduly depressed, endangering the patient's life by the secondary effects of their diminished activity.

Again, I advise against the use of convulsant analeptics like metrazol or picrotoxin in such cases because the dose of the barbiturate was apparently relatively small, and before a considerable amount of vasomotor or respiratory stimulation is obtained with these agents, one often finds oneself tangled up in the problem of managing convulsions.

I have already referred to the fact that most descriptions of the treatment of barbiturate poisoning give one the impression that analeptic drugs should be used in every case in coma. I believe that one of the most important aspects of treatment is the decision as to the kind of cases in which they should be withheld. In laboratory experiments the evidence is fairly clear that animals may survive two to three times an otherwise fatal dose of a barbiturate when treated with picrotoxin. Whether picrotoxin or metrazol save lives in humans, however, has not been very easy to determine. Several years ago I looked into the matter and prepared a report for the Council on Pharmacy and Chemistry of the A.M.A. We compared reports of cases in which the patients were treated with picrotoxin with those of control cases. Authors concluded, for example, that picrotoxin was responsible for the survival of their patients after 5 and 6 Gm. doses of phenobarbital, but the literature revealed cases of survival from similar doses of phenobarbital without picrotoxin. In the experience of the first seven years with picrotoxin, we found twenty-six cases of barbiturate poisoning with a mortality of 15.4 per cent, but the literature showed control groups with a mortality of from 7.6 per cent to 25 per cent. It is not easy, therefore, to make out an entirely satisfactory case for the use of the analeptics, although the results of animal experiments might, for the time being, be taken as sufficient justification for their use.

The case being what it is, however, makes it incumbent upon us to be certain that we do no harm with picrotoxin or the other convulsant analeptics, and in order to avoid doing harm, we should first make fairly certain that the patient is one who stands a fairly good chance of succumbing without the specific aid of an analeptic. Here are a few general rules that are likely to be of some help. Picrotoxin or other convulsant analeptics should be withheld in all cases in which it is possible to elicit such reflexes

as holding the breath, increased breathing, pupillary reactions and knee jerks. These patients recover without picrotoxin. If, as you observe the course, these reflexes begin to vanish, picrotoxin may be started. Picrotoxin should be given to all patients in whom no reflexes can be elicited. A patient who is in coma more than forty hours after one of the rapidly acting barbiturates, such as nembutal or seconal, has almost certainly taken more than an ordinary lethal dose. Such a patient should always receive picrotoxin.

At this point, it might be well if I were to summarize the chief measures employed in barbiturate poisoning. Obviously, in any given case, one uses only those which are indicated: (1) Establish free respiratory exchange by pulling forward the tongue and the lower jaw, by placing in an air way, by suction of the mucus from the respiratory passages. (2) Administer oxygen if there is cyanosis. (3) Stimulate the respiration by caffeine if there is profound respiratory depression. Attempt to raise the blood pressure by means of paredrine or neosynephrine if the blood pressure has reached dangerously low levels without evidence of secondary shock. (4) Treat secondary shock by the usual measures, infusions of plasma in quantities sufficient to raise the blood pressure to levels of 100 or more, or infusions of 5 per cent glucose in saline. Maintain the water balance in the ensuing days by the intravenous injection of 2 or 3 liters of glucose in saline. (5) Use picrotoxin as an analeptic if the conditions for its use exist. (6) Treat with penicillin, 20,000 units intramuscularly every three hours, as a prophylactic against bronchopneumonia. It is not infrequent that the patient recovers from the drug poisoning and then succumbs to a bronchopneumonia.

DR. CATTELL: The topic is now open for general discussion. There are many questions which have been raised. I have a number that I would like to ask Dr. Gold. Is there anyone in the back of the room who would like to start? I think, Dr. Gold, we should have an outline of what would be your procedure in the cases in which picrotoxin is indicated. Would you say a few words on that?

DR. GOLD: If you decide the patient should have picrotoxin, you might use the 0.3 per cent solution, 3 mg. per cc. Give about 10 mg. of picrotoxin intravenously every fifteen to twenty minutes. If the veins are hard to get at, one may use the same dose intramuscularly because the material is well absorbed from the muscle. This dosage plan should be continued until there are signs of excitation in the form of flicking of the fingers, grimaces or abrupt movements of a limb. It is now necessary to maintain that state. This may be done by intramuscular injections of similar doses at longer intervals, the interval being determined by the length of time it takes for signs of excitation to vanish. The reason for the intramuscular dose is that it avoids the high concentration immediately after the injection which sometimes precipitates a convulsion.

DR. CATTELL: Dr. Grace, would you add anything to what Dr. Gold said?

DR. WILLIAM GRACE: I have a few comments with regard to the technical aspects. If the veins are difficult to puncture, we usually set up an infusion and puncture the rubber tubing for each injection. A method which has been used quite extensively is to give a sufficient quantity of picrotoxin every thirty minutes to produce some reaction. As a guide to that we use the return of the corneal reflex or any reflex, and in addition the tone of the muscle. The patients are quite flaccid; and if while the drug is being administered one continually moves the arms or one of the extremities of the patient, one can feel some resistance in the extremities before any twitching or gen-

eralized convulsion is evident. We have used that method in our plan of the management.

DR. GOLD: In relation to the matter of intervals for picrotoxin, it is well to bear in mind the point that picrotoxin in small doses develops its action rather slowly. A dose of 2 mg. of picrotoxin per Kg. of body weight, given intravenously in a cat, will produce a convulsion within fifteen to twenty seconds. Just about one round of the circulation and there it is. A dose of 0.5 mg. per Kg. of body weight, on the other hand, may require as long as ten to fifteen minutes to produce the convulsion. Perhaps a wait of thirty minutes after each injection is not a bad plan to follow. The point is that we want to elicit the full effects of one dose before we give the next dose in order to avoid over-running. The early doses are given at shorter intervals and the later doses at longer intervals.

I should like to warn against the use of muscle tone as a guide to dosage. In severe barbiturate poisoning, picrotoxin produces sudden convulsive flicking of the limbs first. The muscles may still be completely flaccid. Resistance in the muscles develops after doses of picrotoxin too close to, or well within, the range of convulsant doses. If you undertake to increase the tone of the muscles, I am fairly sure that you will frequently over-run and find yourself with a problem of treating a violent convulsion.

VISITOR: Would you care to discuss the treatment of the convulsions produced by picrotoxin in barbiturate poisoning?

DR. GOLD: These convulsions can be controlled by small amounts of ether by inhalation. They may also be controlled by an additional dose of barbiturate. For that purpose, it would be desirable to use a rapidly eliminated barbiturate like pentobarbital-sodium or pentothal-sodium. A dose of 10 mg. might be given intravenously to start with and increased as necessary until the convulsions cease. The needle might be kept in the vein until the full necessary dose is given since the effect of any one dose comes on almost at once.

VISITOR: Why should we worry about the fact that the analeptic whether it is picrotoxin or metrazol, or any other, may produce a convulsion in an overdose during the treatment of barbiturate poisoning? Is there any particular harm in the convulsion? I ask this because metrazol is so commonly used for the specific purpose of producing convulsions in the treatment of schizophrenia.

DR. GOLD: That seems to be a very proper question. I am not certain that the convulsions are injurious. In the study of this problem in the laboratory we obtained some evidence that convulsions may be injurious. For example, in the case of cocaine, it was found that a minimum lethal dose not only causes convulsions but death. When such an animal was treated with barbiturates, the convulsion was prevented and the animal survived. When the dose of cocaine was increased by 50 per cent, the treatment with the barbiturate still prevented the convulsion but the animal died just the same. Cocaine, therefore, has a direct depressant action which seems to be augmented by the convulsions; and when the convulsions are prevented, the animal recovers from an otherwise fatal dose. In such an experiment, therefore, it seems that the convulsions are injurious.

In our studies of strychnine poisoning in the laboratory, we observed another phenomenon. A normal animal poisoned by strychnine shows a rise in blood pressure with each convulsion. When the animal receives a barbiturate, it requires much larger doses of strychnine to produce the convulsion. With these larger doses of strychnine, a reaction appears which is not seen in the normal animal, namely, an initial rise of the blood pressure with a secondary fall to shock levels in association

with each convulsion. I do not know what the situation is in regard to picrotoxin or metrazol, but we must be careful not to carry over the reactions to analeptics on the part of non-narcotized patients to those that are under deep narcosis. The patients poisoned with barbiturates require much larger doses of the analeptics than normal patients, and under those conditions reactions may be obtained which one never sees in normal people receiving the smaller convulsant doses. In view of such experimental observations, it would seem to be wise to avoid producing convulsions by the analeptic drugs in barbiturate poisoning until there is more evidence that the convulsions under those conditions are not harmful. You see, we know a good deal about the reactions of the normal person to a convulsant dose of the analeptic, and of the normal person to a narcotizing dose of the barbiturate, but we are without sufficient information about the reactions of the patient poisoned by the combination of several times the fatal dose of both the barbiturate and the analeptic.

DR. WALTER MODELL: Why do you prefer picrotoxin to metrazol, which, I think, works well in animals?

DR. GOLD: Metrazol is quite satisfactory but, using several criteria of efficiency, the experiences in the laboratory tend to favor picrotoxin. Metrazol has a somewhat shorter duration of action than picrotoxin, and this might necessitate more frequent doses in order to maintain the subconvulsive state. I think these arguments are not very strong and I am not sure that their difference is very important. When we have metrazol available, there would be no need to go far out of our way to secure picrotoxin.

DR. JANET TRAVELL: Would not metrazol have an advantage in that its effects after intravenous injections are not delayed as in the case of picrotoxin?

DR. GOLD: That sounds like an advantage.

DR. TRAVELL: You would not be so likely to over-run.

DR. GOLD: That is true.

DR. CATTELL: A recent report by a group of British workers appeared in the *Journal of Pharmacology*, in which a series of analeptics was investigated in relation to the time of recovery of mice from large doses of barbiturates. Picrotoxin was found to stand way ahead of the others, and that is in line with the results of several other studies.

STUDENT: If a person has been in coma a long time from a short-acting barbiturate, why give picrotoxin at all?

DR. GOLD: Are you referring to my statement that a patient poisoned by a short-acting barbiturate, who is seen in coma forty hours later, should be treated with picrotoxin?

STUDENT: Yes.

DR. GOLD: The reason is that patients, poisoned by borderline fatal doses of the short-acting-barbiturates, almost invariably regain some consciousness within twenty-four to thirty-six hours. If there is still deep coma at this time, it is likely that they have had much more than the single lethal dose. That, by definition, means that they will not recover without some help.

VISITOR: Does picrotoxin or metrazol merely enable a person to recover from an otherwise fatal dose of barbiturate or does it also increase the speed of recovery? If it also accelerates recovery, then it might seem wise to use these drugs even in cases in which it is likely that they will recover without the analeptic.

DR. GOLD: There is some evidence that animals recover from a barbiturate more quickly when treated with the analeptic than those allowed to recover spontaneously. I am inclined, however, to advise against their use merely to accelerate recovery because of the danger inherent in

the use of large doses of these convulsant agents. I believe that the possibilities for harm are greater than those for good.

INTERNE: Have you ever used strychnine for the treatment of barbiturate poisoning?

DR. GOLD: I have not used it myself in human cases, but it has been used, and in doses of 2 mg. or 1/30 gr. subcutaneously at intervals of one or two hours. Dr. Travell and I published some papers several years ago on experiments with strychnine as an antidote to poisoning by alcohol and barbiturates. Although it was possible to produce hyperexcitability and convulsions in the narcotized animals, strychnine did not prove very effective in saving life. There are other experimental studies in the literature which also rank strychnine fairly low down on the list of analeptics.

STUDENT: What sort of supportive treatment do you give these patients who are in coma for many hours? You mentioned some of them being in coma as long as forty hours or more.

DR. GOLD: Supportive treatment is not very important in the first twenty-four hours or so, and it can be managed by intravenous infusions of 5 per cent glucose in saline. It becomes of greater importance, however, when coma lasts much longer, four or five days, as is the case after massive doses of the barbiturates and after some of the long-acting barbiturates. In these cases supplementary measures might be helpful, such as, plasma infusions and large doses of vitamin supplements. It might also be well to consider the use of intravenous protein hydrolysates. I do not know of any experience with the use of these in barbiturate poisoning.

DR. CATTELL: In severe poisoning by the barbiturates, the terminal picture is one of peripheral vascular failure. What do you think of the value of picrotoxin for improving the circulation by maintaining the central nervous system functions at a higher level, even though it does not affect the circulation directly?

DR. GOLD: I am inclined to think picrotoxin is of value against the circulatory depression through its action on the central nervous system.

DR. CATTELL: You mentioned the use of epinephrine. You did not state whether you would use that in severe poisoning.

DR. GOLD: I mentioned paredrine and neosynephrine. They are preferable to epinephrine because they are less apt to cause marked acceleration of heart and secondary vasodepression. They are useful for raising the blood pressure in the milder cases of barbiturate poisoning with vasomotor depression. These are patients in whom the color is fairly normal, the skin is warm, but the blood pressure is down to such levels as 80 or 70 systolic. In them, these drugs boost the pressure and accelerate the circulation.

It is quite another matter, however, if the patient is in secondary shock. In such an individual, the blood pressure is apt to be very low, the skin cold and clammy, the neck veins collapsed, and the respiration profoundly depressed. The peripheral constrictors are not apt to be of any value here. These are to be treated in much the same way as any case of secondary shock, with oxygen and plasma infusions in quantities sufficient to raise the pressure to more satisfactory levels and to abolish the symptoms of circulatory collapse.

DR. MODELL: I want to ask Dr. Gold a question about the effect of picrotoxin on respiration. Would you use picrotoxin if the respiration were seriously depressed, but the other signs which you listed as indications for picrotoxin were not there?

DR. GOLD: In some cases I would. There are always borderline cases in which a decision is difficult to make. There are instances in which the general picture is that of moderately deep narcosis from which

one might expect the patient to recover without any specific treatment, but the respiration is so depressed that one can hardly see the patient breathing. Picrotoxin might well be considered for such a case, but with the warning that this patient may only be lightly narcotized and may, therefore, be very sensitive to picrotoxin. The very first dose may produce a fit.

DR. MODELL: The impression is that the analeptics are good respiratory stimulants. They are frequently used for that purpose alone.

DR. GOLD: Some of the analeptics are good respiratory stimulants. The case of picrotoxin presents special features. In the normal animal it produces respiratory stimulation at the dosage level which causes fits, but in the animal under the influence of large doses of barbiturates, it produces respiratory stimulation at a dosage level much below that which causes fits. The development of such a dosage differential is partly responsible for the usefulness of picrotoxin against depressed respiration in the narcotized individual.

DR. MODELL: Dr. Gold, you mentioned patients with barbiturate poisoning who succumb in spite of the most vigorous kind of treatment applied promptly and under the most favorable conditions. What seems to be the trouble in these cases?

DR. GOLD: I am not sure of the difficulty there. It looks as though none of the current treatment for barbiturate poisoning directly reverses the basic disturbances in the metabolism of the cells caused by barbiturates. In point of fact, we are not sure what that basic injury is. There are some studies which indicate that the barbiturates interfere with dehydrogenase activity, thereby blocking intermediary sugar metabolism. The oxidation of glucose, pyruvate and lactate is impaired, but apparently not that of succinate. These observations have been put to the test and there are suggestive indications that succinates may reverse barbiturate poisoning in animals. There is also the suggestion that sodium succinate given in an intravenous infusion of a 10 per cent solution in a dose of about 20 Gm. may be of some value in humans, but the evidence is still far from satisfactory. In any case, it seems likely that after massive doses of barbiturate some metabolic disturbance is produced which is irreversible by any of the current means of treatment. Our present antidote measures do not appear to function at the level of the specific mechanism of the cellular poisoning.

DR. E. SHORR: It is worth while pointing out that there is considerable doubt about the effectiveness of sodium succinate in barbiturate poisoning as well as about the way in which such benefit is achieved. In our own laboratory, Furchgott and I have observed an enhancement of oxygen consumption of brain cortex with fairly large concentrations of succinic acid *in vitro*. This effect, no matter what the concentration, lasts only one hour. Furthermore, it achieves no increase in acetyl choline formation which would be expected from stimulation of brain metabolism by a normal substrate. Experiments on a variety of other tissues under succinate stimulation have clearly demonstrated that succinate is unable to benefit any aspect of intermediary metabolism. In fact it may actually depress the oxidation of normal substrates and thereby interfere with normal metabolic processes. However, there seems to be no doubt that in some instances the administration of sodium succinate has been of benefit in barbiturate poisoning as well as in experimental shock, but the benefit seems to be attributable not to the succinate but to the sodium ion, since equal benefit has been obtained from the administration of sodium bicarbonate. Any state, such as barbiturate poisoning, which leads to anoxia results in increased lactic acid in the blood

and a fall in carbon dioxide combining power and blood pH. The sodium ion in sufficient amounts would overcome acidosis and the deleterious effects associated with this condition. The amount of sodium required to correct the acidosis should be determined by frequent estimations of carbon dioxide combining power.

DR. CATTELL: I remember Dr. Helpern mentioned the brain lesion in the area of the globus pallidus in long lasting barbiturate poisoning similar to that of carbon monoxide. If the injury proceeded that far, I do not think there would be much chance of recovery.

DR. GOLD: Yes, some of the irreversible poisonings by barbiturates probably involve this symmetrical necrosis of the globus in consequence of long-lasting anoxia. Others may develop the type of diffuse cerebral and cerebellar injury which we have seen in some of the animal experiments. In one study a barbiturate was found to produce permanent motor and postural changes associated with histological lesions in the brain. We do not know whether these also result from the sustained anoxia.

DR. TRAVELL: In view of these conditions, should not oxygen inhalation be considered under the heading of supportive treatment in barbiturate poisoning?

DR. GOLD: Yes, I believe oxygen should be used freely and especially in those cases in which there seems to be the slightest question of inadequate respiratory exchange.

SUMMARY

DR. GOLD: Cases of acute poisoning by the barbiturates are becoming more and more numerous. The following measures for the treatment of acute barbiturate poisoning were explored in the conference this afternoon: Establishment of a free airway, suction of mucus from the upper respiratory passages, oxygen inhalation, caffeine for respiratory stimulation, paredrine and neosynephrine for vasomotor stimulation, infusions of glucose in saline, infusions of plasma, vitamin supplements, prophylactic penicillin, and specific analeptics such as metrazol and picrotoxin.

The broad principles regulating the application of these measures were outlined, but emphasis was placed on the need for varying the procedures according to the indications of the particular case. It is often impossible to ascertain the precise dose of barbiturate which the patient has taken. The kind of treatment needs, therefore, to be decided on the basis of the depth of the narcosis and on the question of whether all the poison has already been absorbed. Criteria for determining these two points were discussed. Attention was called to the fact that a large proportion of the cases of barbiturate poisoning survive without specific antidotes, and to the fact that the use of the convulsant antidotes is not without danger. A distinction needs to be drawn between depression due to the direct action of the drug and that due to the secondary effects of impaired respiratory exchange. A patient profoundly depressed as the result of the anoxia may be very sensitive to picrotoxin and may develop a convulsion after a relatively small dose, while the patient similarly depressed as the result of a massive dose of the barbiturate may require several times the normal fatal dose of picrotoxin to produce stimulation. Picrotoxin seems to be the antidote of choice. The discussion attempted to crystallize the conditions under which it may be used and the most favorable plans for its administration.

Book Reviews

In 1944, twelve American artists, John Steuart Curry, Fred Shane, Manuel Tolegian, Ernest Fiene, Franklin Boggs, Robert Benney, Joseph Hirsch, Lawrence Beall Smith, Howard Baer, Francis Criss, Peter Plume and Marion Greenwood, sponsored by Abbott Laboratories, set out to record in paintings and sketches the work of the Army Medical Department. They covered not only the activities at home but the various theatres of operations as well, ranging from the front lines to the rear echelons, from Saipan to Normandy. Their results in time became the Abbott Collection of Paintings, now owned by the United States Government and widely acclaimed both for its pictorial excellence and graphic realism.

The present volume* contains 137 pieces with captions from this collection, 118 being well reproduced in full color. A brief history of each artist, his experiences with the troops and his enthusiastic impressions of Army medicine at work, complete the book. The pages are large, the paper good and the typography excellent.

For those who want a visual reminder, or for those who would like a layman's impressionistic survey of the Army Medical Corps in World War II, this volume can be recommended.

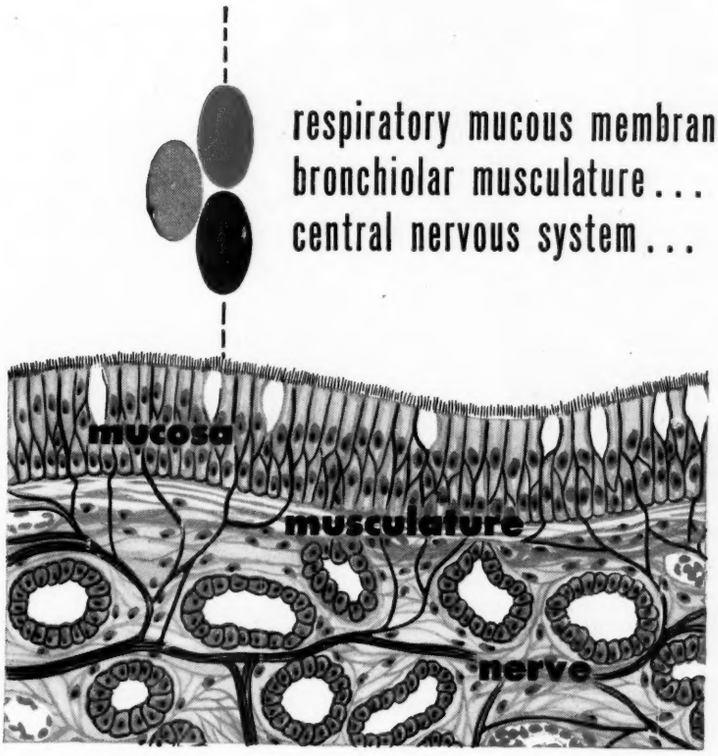
*Men without Guns. By De Witt MacKenzie. Cloth. Pp. 47, with 137 illustrations. Philadelphia and Toronto, 1945. The Blakiston Company. *Price* $5.00

"An Introduction to Essential Hypertension"* is designed to introduce the busy practitioner to the field of hypertension. No efforts have been spared to make the introduction an easy one. These include frequent subject headings, short paragraphs, and the generous use of heavy type to emphasize both the important points in the text and the summaries at the end of each chapter.

The contents are divided into eight chapters. In the first, the subject is defined and the normal regulation of blood pressure is considered. There follow succint discussions on etiology and mechanism, physiology, pathology, clinical aspects, prognosis, diagnosis and treatment. Many important references and a moderately complete index are included. While the subject is a large one, the author has succeeded in briefly covering its most prominent facets with clarity and moderation.

As an introductory volume, the book can certainly be recommended to the practitioner and medical student.

*An Introduction to Essential Hypertension. By Richard F. Heridon, M.D., F.A.C.P. Fabrikoid. Pp. 104, with 7 illustrations. Springfield, Illinois, 1946. Charles C. Thomas. *Price* $2.50.



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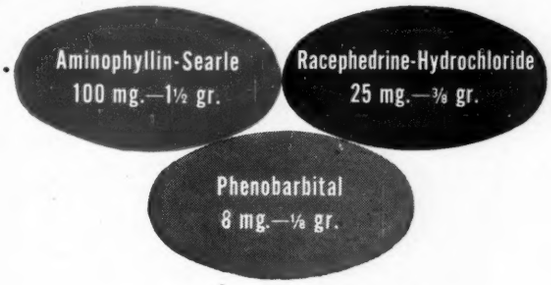

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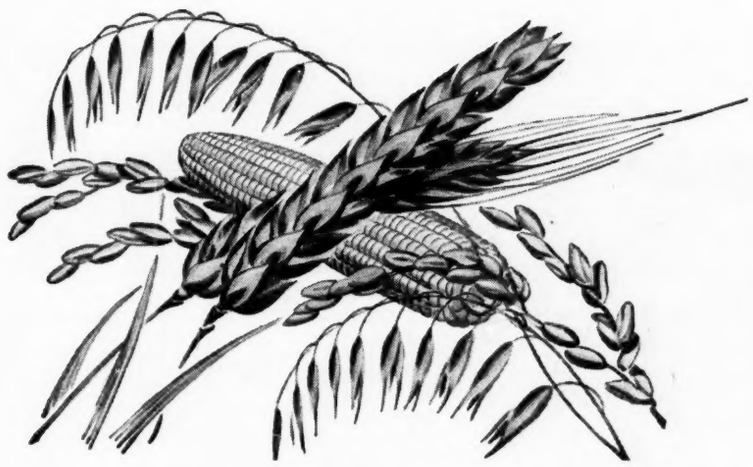

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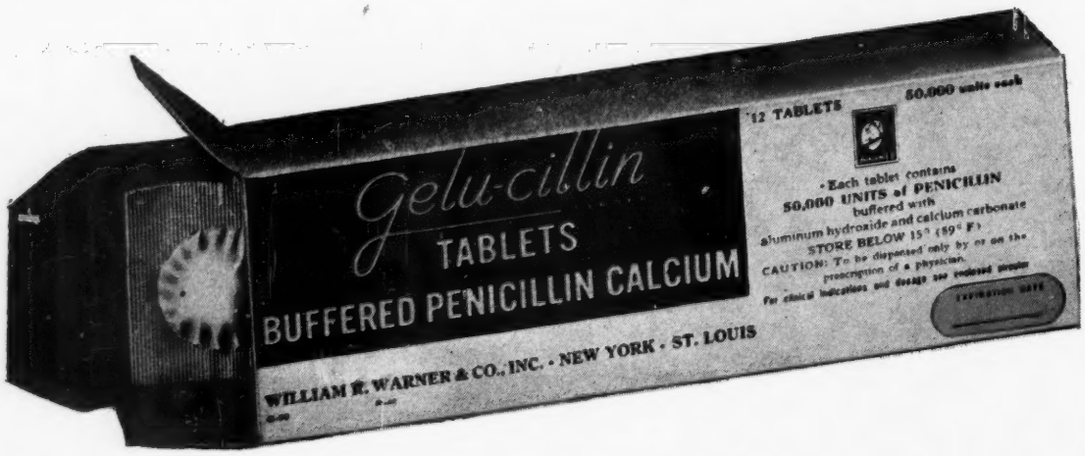

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